Epidemics 34 (2021) 100432

Contents lists available at ScienceDirect

Epidemics

journal homepage: www.elsevier.com/locate/epidemics

Accounting for cross-immunity can improve forecast accuracy during influenza epidemics

Rahil Sachak-Patwa [a,*], Helen M. Byrne [a], Robin N. Thompson [a,b,c]

[a] Mathematical Institute, University of Oxford, Andrew Wiles Building, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG, UK
[b] Christ Church, University of Oxford, St Aldates, Oxford, OX1 1DP, UK
[c] Present address: Mathematics Institute, University of Warwick, Zeeman Building, Coventry, CV4 7AL, UK

ARTICLE INFO

Keywords:
Mathematical modelling
Influenza forecasting
Real-time forecast
Cross-immunity
2009 H1N1 pandemic

ABSTRACT

Previous exposure to influenza viruses confers cross-immunity against future infections with related strains. However, this is not always accounted for explicitly in mathematical models used for forecasting during influenza outbreaks. We show that, if an influenza outbreak is due to a strain that is similar to one that has emerged previously, then accounting for cross-immunity explicitly can improve the accuracy of real-time forecasts. To do this, we consider two infectious disease outbreak forecasting models. In the first (the "1-group model"), all individuals are assumed to be identical and cross-immunity is not accounted for. In the second (the "2-group model"), individuals who have previously been infected by a related strain are assumed to be less likely to experience severe disease, and therefore recover more quickly, than immunologically naive individuals. We fit both models to estimated case notification data (including symptomatic individuals as well as laboratory-confirmed cases) from Japan from the 2009 H1N1 influenza pandemic, and then generate synthetic data for a future outbreak by assuming that the 2-group model represents the epidemiology of influenza infections more accurately. We use the 1-group model (as well as the 2-group model for comparison) to generate forecasts that would be obtained in real-time as the future outbreak is ongoing, using parameter values estimated from the 2009 epidemic as informative priors, motivated by the fact that without using prior information from 2009, the forecasts are highly uncertain. In the scenario that we consider, the 1-group model only produces accurate outbreak forecasts once the peak of the epidemic has passed, even when the values of important epidemiological parameters such as the lengths of the mean incubation and infectious periods are known exactly. As a result, it is necessary to use the more epidemiologically realistic 2-group model to generate accurate forecasts. Accounting for cross-immunity driven by exposures in previous outbreaks explicitly is expected to improve the accuracy of epidemiological modelling forecasts during influenza outbreaks.

1. Introduction

Three major influenza pandemics occurred in the 20th century, in 1918, 1957, and 1968 (Kilbourne, 2006). Each pandemic resulted in over one million deaths, with the death toll of the 1918 Spanish Flu pandemic estimated to be 50 million people (Johnson and Mueller, 2002). In 2009, reassortment of North American and Eurasian swine viruses generated a new strain of H1N1, triggering the first influenza pandemic of the 21st century (Trifonov et al., 2009; Christman et al., 2011). The virus is believed to have originated in Mexico in April 2009, and then spread rapidly across the globe, reaching 43 countries by May that year (Fraser et al., 2009; Trifonov et al., 2009). The case fatality rate due to the virus was lower than that of previous pandemics in the 20th century (Kamigaki and Oshitani, 2009). However, the scale of the pandemic, with estimates that 11%–21% of the global population contracted the virus, led to a significant burden on healthcare systems (Kelly et al., 2011).

Influenza A viruses mutate over time, either due to antigenic drift, where a small mutation in the genes of the virus leads to changes in the surface proteins producing a closely related strain, or, antigenic shift, an abrupt, major change in the virus due to recombination and reassortment, resulting in new surface proteins (Bouvier and Palese, 2008; Kim et al., 2018). A new form of the virus that has emerged due to drift is likely to have similar antigenic properties to the original virus, and thus individuals who were infected with the original virus may have acquired some immunity to the altered virus. However, when antigenic shift occurs, many individuals are likely to have little or no immunity

* Corresponding author.
E-mail address: rahil.sachak-patwa@maths.ox.ac.uk (R. Sachak-Patwa).

https://doi.org/10.1016/j.epidem.2020.100432
Received 5 July 2020; Received in revised form 11 December 2020; Accepted 15 December 2020
Available online 17 December 2020

to the new virus (depending on their lifetime history of infection). Due to the random nature of the emergence of new influenza strains, it is not currently possible to predict when future pandemics will occur, and which strains will cause these pandemics (Neumann and Kawaoka, 2019). However, mathematical models have been used extensively for forecasting and informing public health measures when outbreaks are ongoing (Ferguson et al., 2006; Hall et al., 2007; Nishiura, 2011; Ohkusa et al., 2011; Tizzoni et al., 2012; Biggerstaff et al., 2016; Thompson and Brooks-Pollock, 2019).

The most basic infectious disease outbreak models assume that individuals have similar characteristics (Chowell et al., 2006; Bettencourt and Ribeiro, 2008). More complex models account for differences between individuals. For example, in many studies that aim to determine optimal vaccination strategies, populations are split into low-risk and high-risk groups (Gani et al., 2005; Dushoff et al., 2007), and spatial heterogeneity can be incorporated by partitioning individuals according to their location (Longini Jr. et al., 2004; Ohkusa et al., 2009). Commonly, due to different contact rates between individuals of different ages, as well as varying case fatality rates between age groups, age-structured models are used (Chowell et al., 2009; Medlock and Galvani, 2009; Glasser et al., 2010; Klepac et al., 2018; Davies et al., 2020; Thompson, 2020b). Models of influenza transmission that incorporate evolutionary and multi-strain dynamics (He et al., 2015; Yang et al., 2015; Du et al., 2017), as well as phylodynamics (accounting for temporal changes in pathogen phylogenies), have also been considered (Grenfell, 2004; Koelle et al., 2006; Frost et al., 2015).

Other types of heterogeneity also play an important role in the dynamics of influenza outbreaks. Previous exposure to an influenza virus confers homosubtypic cross-immunity to antigenically related strains of the original virus due to cross-reactive neutralising antibodies (Grebe et al., 2008; Kreijtz et al., 2011; Krammer, 2019; Padilla-Quirarte et al., 2019). These neutralising antibodies, predominantly against haemagglutinin (HA) proteins on the surface of the virus, block viral entry to the host cell (Sym et al., 2009; Huang et al., 2013). It has also been suggested that cross-protective non-HA antibody immunity may lead to reduced disease severity (Fang et al., 2011). Neuraminidase (NA) specific antibodies have also been shown to reduce influenza viral titres, morbidity, and virus shedding (Schulman et al., 1968; Murphy et al., 1972; Couch et al., 1974; Webster et al., 1988; Epstein et al., 1993; Mozdzanowska et al., 1999). As well as homosubtypic immunity, there is evidence of heterosubtypic immunity, namely cross-protection generated by prior exposure to a different but related influenza subtype (Nguyen et al., 2007; Grebe et al., 2008; Fox et al., 2017). Cross-immunity – homosubtypic and/or heterosubtypic – may explain why there has not been an influenza pandemic as severe as the 1918 pandemic in the last century (Thompson et al., 2019).

A significant proportion of elderly individuals carried pre-existing immunity (due to cross-reactive anti-HA antibodies) to the influenza strain that was responsible for the 2009 pandemic (Hancock et al., 2009; Xing and Cardona, 2009; Bandaranayake et al., 2010; Hardelid et al., 2010; Gostic et al., 2019). This may be due to the similarities between the 2009 H1N1 virus and the 1918 Spanish Flu virus, as viral descendants of the 1918 Spanish Flu virus continued to circulate until the 1957 pandemic (Skountzou et al., 2010; Xu et al., 2010). The suggestion that immunity was due to previous infections that occurred decades earlier implies that this form of cross-immunity is likely to be lifelong (Yu et al., 2008). The consequences of pre-existing immunity can be seen in the age distribution of infected individuals in Japan in the 2009 pandemic, where only a small proportion of the individuals who sought medical attention were elderly (Mizumoto et al., 2013). A number of studies in animals have also shown that prior infection with seasonal H1N1 strains have been able to provide substantial protection against infection with the 2009 H1N1 pandemic virus (Ellebedy et al., 2010; Kash et al., 2010; Laurie et al., 2010; Ellebedy et al., 2011). As well as the heterogeneity between hosts in infection risk and age mentioned previously, models in which populations are structured according to whether or not individuals carry pre-existing immunity can also be formulated (Andreasen et al., 1997; Martcheva and Pilyugin, 2006; Reluga et al., 2008; Penman et al., 2016; Thompson et al., 2019).

In this paper, our attention is directed towards how cross-immunity (either homosubtypic or heterosubtypic) affects the predictability of epidemics. We use mathematical models to investigate whether or not it is necessary to account for cross-immune individuals in the population when forecasting the dynamics of future influenza epidemics. We consider two epidemiological models. In the first, cross-immunity is ignored (the "1-group model"). In the second, more epidemiologically realistic model (the "2-group model"), individuals with and without cross-immunity are accounted for explicitly.

First, we estimate the values of the parameters of each model (specifically, the transmission rate and the effective population size) using data from the 2009 H1N1 influenza epidemic in Japan. We then consider a synthetic future influenza epidemic of an antigenically similar strain, simulated using the more epidemiologically realistic 2-group model. We explore whether or not accurate forecasts of this epidemic can be obtained in real-time. If uninformative priors are used and parameters are estimated in real-time, even the more realistic 2-group model is unable to generate accurate forecasts of the remainder of the epidemic before the peak occurs. This motivates us to incorporate information from the 2009 epidemic to set informative priors. We show that forecasts made using the 1-group model in advance or at the start of a future epidemic are inaccurate, even if informative priors are used, because that model does not account for differing levels of cross-immunity between the starts of the 2009 epidemic and the future epidemic. We then use both information from the 2009 epidemic and data obtained as the future outbreak is ongoing to generate real-time forecasts using the 1-group and 2-group models. Early in the outbreak, only the 2-group model can provide accurate forecasts of the remainder of the epidemic. For that reason, cross-immunity should be included in epidemiological forecasting models whenever a large influenza outbreak is related to an antigenically similar strain that has previously caused a major epidemic.

2. Methods

2.1. Data

Our analysis involves case notification data from the 2009 H1N1 influenza epidemic in Japan comprising the estimated numbers of weekly cases seeking medical attention in that country. These nationwide data were based on sentinel data from 4800 hospitals, extrapolated to the total number of medical facilities in Japan (Nishiura, 2011; Omori and Nishiura, 2011). The data were acquired from Fig. 1 of the analysis by Nishiura (2011) using the data extraction tool https://automeris.io/WebPlotDigitizer/ and the extracted data are available in Supplementary Data S1. The data represent the numbers of patients per week who sought medical attention and met one or more of the following criteria: (i) acute course of illness, (ii) fever higher than 38°C, (iii) cough, sputum or breathlessness (symptoms of upper respiratory infection), (iv) general fatigue, and (v) positive laboratory diagnosis.

It was estimated that 23.5% of the Japanese population were infected during the epidemic, and that 16.1% were infected and sought medical attention (Mizumoto et al., 2013). Therefore $(23.5-16.1)/23.5 = 31.5\%$ of infected individuals did not seek medical attention. We assume that those infected individuals who did not seek medical attention suffered mild symptoms of influenza because they were cross-immune to the virus (see Discussion). Hence, extrapolating to the rest of the population and assuming that the susceptibility of hosts is unaffected by cross-immunity, we assume when fitting the 2-group model that 31.5% of the population were cross-immune to the virus and that 68.5% were immunologically naive (i.e. had not previously acquired cross-immunity to the 2009 H1N1 pandemic strain, as they had not

been infected by a previous antigenically similar strain of the virus). However, we also test the robustness of our results to this assumption by conducting analyses for different proportions of the population that are cross-immune (Supplementary Information Section S.1).

2.2. Models

We consider two models characterising influenza outbreaks. In the first (the 1-group model), which is the commonly used SEIR model (Anderson and May, 1991; Mills et al., 2004; Chowell et al., 2006; Chen and Liao, 2008; Thompson et al., 2016), cross-immunity is neglected. In the second (the 2-group model), individuals who have been infected previously by a related strain are assumed to recover from infection more quickly than individuals who are immunologically naive. Schematics illustrating the compartmental structures of both models are shown in Fig. 1.

2.2.1. 1-group model

The 1-group SEIR model is described by the following differential equations, in which individuals are either (S)usceptible and available for infection, (E)xposed (i.e. infected but not yet infectious or symptomatic), (I)nfectious or (R)emoved:

$$\frac{dS}{dt} = -\frac{\beta}{N} SI, \tag{1}$$

$$\frac{dE}{dt} = \frac{\beta}{N} SI - \kappa E, \tag{2}$$

$$\frac{dI}{dt} = \kappa E - \mu I, \tag{3}$$

$$\frac{dR}{dt} = \mu I. \tag{4}$$

In this model, the infection rate is governed by the parameter β, the mean latent period is $1/\kappa$ weeks and the mean infectious period is $1/\mu$ weeks. The basic reproduction number under the 1-group model is given by

$$R_0 = \frac{\beta}{\mu}. \tag{5}$$

Following Cintrón-Arias et al. (2009), the number of recorded cases in week j (recorded at the end of that week), where j is the integer number of weeks since the epidemic began, is given by

$$C(j) = \int_{j-1}^{j} \kappa E \, dt. \tag{6}$$

The constant value $S + E + I + R = N$ represents the effective population size. Since pathogens are most likely to be transmitted locally, individuals in distant locations are not available for infection and so N is expected to be smaller than the true population size (Gart, 1968; Pouillot et al., 2008). In Table 1(a), we list the parameters that appear in Eqs. (1)–(4) and estimates of their values for the Japanese 2009 H1N1 epidemic (see also Sections 2.3 and 3.1).

2.2.2. 2-group model

The 2-group model is an extension of the standard SEIR model in which immunologically naive and cross-immune individuals are distinguished between. The 2-group model is given by the following system of differential equations:

$$\frac{dS_I}{dt} = -\frac{\beta}{N} S_I(I_I + I_N), \tag{7}$$

$$\frac{dE_I}{dt} = \frac{\beta}{N} S_I(I_I + I_N) - \kappa E_I, \tag{8}$$

$$\frac{dI_I}{dt} = \kappa E_I - \mu_I I_I, \tag{9}$$

$$\frac{dR_I}{dt} = \mu_I I_I, \tag{10}$$

$$\frac{dS_N}{dt} = -\frac{\beta}{N} S_N(I_I + I_N), \tag{11}$$

$$\frac{dE_N}{dt} = \frac{\beta}{N} S_N(I_I + I_N) - \kappa E_N, \tag{12}$$

$$\frac{dI_N}{dt} = \kappa E_N - \mu_N I_N, \tag{13}$$

$$\frac{dR_N}{dt} = \mu_N I_N. \tag{14}$$

The basic reproduction number under the 2-group model is given by

$$R_0 = \frac{\beta\nu}{\mu_I} + \frac{\beta(1-\nu)}{\mu_N}, \tag{15}$$

where the two terms represent the relative contributions from the cross-immune and immunologically naive groups respectively. The first term represents the expected number of infections generated by a single infected individual with previously acquired cross-immunity (assuming that no other individuals are infected at the time of introduction), scaled by the proportion of individuals who previously acquired cross-immunity. The second term represents the expected number of infections generated by a single infected individual who was previously immunologically naive, scaled by the proportion of individuals who were previously immunologically naive. See Supplementary Information Section S.2 for details of the calculation.

There is evidence that cross-immunity in the elderly population reduced the disease severity of the 2009 H1N1 pandemic virus (Miller et al., 2010; Chen, 2010). We assume that cross-immune individuals experience less severe disease and therefore typically recover more quickly than immunologically naive individuals (i.e. $1/\mu_I < 1/\mu_N$). Cross-immunity is therefore partial: it does not reduce disease completely. To isolate this effect alone on the predictability of epidemics, in this model it is assumed that cross-immune and naive individuals are otherwise identical. In particular, we assume that susceptible cross-immune individuals and susceptible naive individuals are equally likely to be infected.

We assume that only cases of severe disease (i.e. infected individuals who were previously immunologically naive) report infection, so that the number of recorded cases in week j is given by

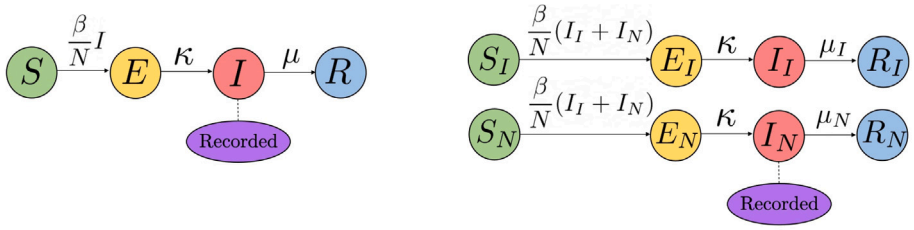
$$C(j) = \int_{j-1}^{j} \kappa E_N \, dt. \tag{16}$$

Since we assume that only immunologically naive individuals report infection, the infectious period of immunologically naive individuals in the 2-group model is assumed to be identical to the infectious period in the 1-group model (i.e. $1/\mu_N = 1/\mu$).

Denoting the proportion of individuals in the population who are cross-immune by ν, we have that $S_I + E_I + I_I + R_I = \nu N$ and $S_N + E_N + I_N + R_N = (1-\nu)N$, where $S_I + E_I + I_I + R_I + S_N + E_N + I_N + R_N = N$ is the total effective population size. In Table 1(b), we list the parameters that appear in Eqs. (7)–(14) and estimates of their values for the Japanese 2009 H1N1 epidemic (see also Sections 2.3 and 3.1).

2.3. Parameter estimation and forecasting

When fitting the models to each dataset in this study (either the data from the 2009 H1N1 epidemic in Japan or simulated future outbreak data), the transmission rate parameter, β, and effective population size, N, are estimated using Markov chain Monte Carlo (MCMC) with the Metropolis–Hastings algorithm (Hastings, 1970). All other parameters are assumed to be known. A likelihood function is used in which it is assumed that the differences between the data and model forecasts (where the differences are due to noise not accounted for in the models) are normally distributed, and that this noise scales with the square root of the size of the data (i.e. the number of cases). We estimate the noise scaling parameter, σ, in the likelihood function, by fitting each model to data from the 2009 Japan epidemic using a least squares approach (Cintrón-Arias et al., 2009). The value of σ is then fixed throughout this study. An analysis of the residuals (the scaled differences between each data point and the corresponding model values) is given in Supplementary Information Section S.3, justifying the square root noise scaling assumption. In each MCMC simulation, we perform 2×10^5 sampling iterations, discard the first 10^4 iterations



(a) 1-group model (b) 2-group model

Fig. 1. Schematics illustrating the structures of the 1-group and 2-group models. In both cases, the population is compartmentalised into susceptible S, exposed (infected but not yet infectious) E, infectious I, and recovered R classes. In the 2-group model, cross-immune and immunologically naive individuals are distinguished between, and it is assumed that only infected naive individuals are recorded in case notification data (with perfect reporting). In the 1-group model, there is no distinction between cross-immune and immunologically naive individuals, and it is assumed that all infected individuals are recorded in case notification data (again with perfect reporting).

Table 1
Descriptions of parameters of the 1-group and 2-group models and estimates of their values for the Japanese 2009 H1N1 epidemic.

Parameter	Description	Values	Source
β	Transmission rate	1.644 Weeks^{-1}	Estimated from data (Fig. 3)
N	Effective population size	3.072×10^7	Estimated from data (Fig. 3)
$1/\kappa$	Latent period	4/7 Weeks	Tuite et al. (2009)
$1/\mu$	Infectious period	1 Week	Tuite et al. (2009)
$C(0)$	Initial number of recorded cases	24073	Nishiura (2011)
(a): 1-group model			
Parameter	Description	Values	Source
β	Transmission rate	1.947 Weeks^{-1}	Estimated from data (Fig. 3)
N	Total effective population size	4.660×10^7	Estimated from data (Fig. 3)
ν	Cross-immune fraction	0.3149	Estimate based on Mizumoto et al. (2013)
$1/\kappa$	Latent period	4/7 Weeks	Tuite et al. (2009)
$1/\mu_I$	Infectious period (cross-immune individuals)	3/7 Weeks	Estimate based on Fielding et al. (2013)
$1/\mu_N$	Infectious period (naive individuals)	1 Week	Tuite et al. (2009)
$C(0)$	Initial number of recorded cases	24073	Nishiura (2011)
(b): 2-group model			

as the 'burn-in' period and record every 100 iterations thereafter to reduce autocorrelation. Further details are given in Supplementary Information Section S.4.

When making forecasts in real-time after $t = m$ weeks of the epidemic, we calibrate our model forecasts with the observed data for weeks $0, 1, \ldots, m$ of the epidemic, estimating model parameters using the method described above. To generate forecasts, we use these estimated model parameters and project the models forwards, starting in week m with initial conditions estimated based on the number of cases observed in weeks $0, 1, \ldots, m$ (for details, see Supplementary Information Section S.5).

To compare different model forecasts throughout this study, we use the deviance information criterion (DIC) (Spiegelhalter et al., 2002). Details and DIC values are given in Supplementary Information Section S.6.

2.4. Modelling the size of the cross-immune population between epidemics

For the 2-group model, we assume that all immunologically naive individuals infected during an earlier epidemic acquired cross-immunity to antigenically related strains of the virus. Individuals who were cross-immune at the beginning of the 2009 epidemic, as well as individuals who were infected during the 2009 epidemic, are therefore assumed to be cross-immune. Furthermore, we assume that cross-immunity to related strains is lifelong (Yu et al., 2008). Using these assumptions, we can model the cross-immune fraction of the population over the years between the end of a first epidemic and the start of a future epidemic of a related strain of influenza accounting for population turnover (births and natural deaths). This is important, since the period between major influenza epidemics (or pandemics) is typically many years (Kilbourne, 2006). Further details are given in Supplementary Information Section S.7. We seed the future epidemics by assuming that there are 10,000 recorded cases in the first week from which we generate forecasts (three orders of magnitude smaller than the estimated effective population sizes). When using the 2-group model to forecast future epidemics, we assume that the cross-immune fraction of the population is known exactly.

2.5. Approaches to forecasting a future epidemic

We use the 1-group and 2-group models (Fig. 1) to explore the accuracies of three different potential forecasting approaches (see Fig. 2 for a schematic illustrating these approaches). Specifically, we consider: generating a forecast using case notification data collected in real-time but without incorporating prior information from an earlier epidemic (Strategy 1); generating a forecast in advance of the epidemic, but using the previous epidemic as prior information (Strategy 2), and; generating a forecast using case notification data collected in real-time and also using the previous epidemic as prior information (Strategy 3).

3. Results

3.1. Fitting models to the 2009 H1N1 influenza epidemic in Japan

We fit the 1-group and 2-group models to data from the 2009 H1N1 influenza epidemic (Fig. 3(a), (b)). The shaded regions represent the 95% prediction credible intervals (CrIs) of epidemic trajectories based on the posterior distributions of fitting parameters β and N. Since the 1-group model does not account for infected but unrecorded individuals, the estimated parameters for the model represent a lower effective population size N than the for the 2-group model, while the estimated basic reproduction numbers R_0 are similar (Fig. 3(c),

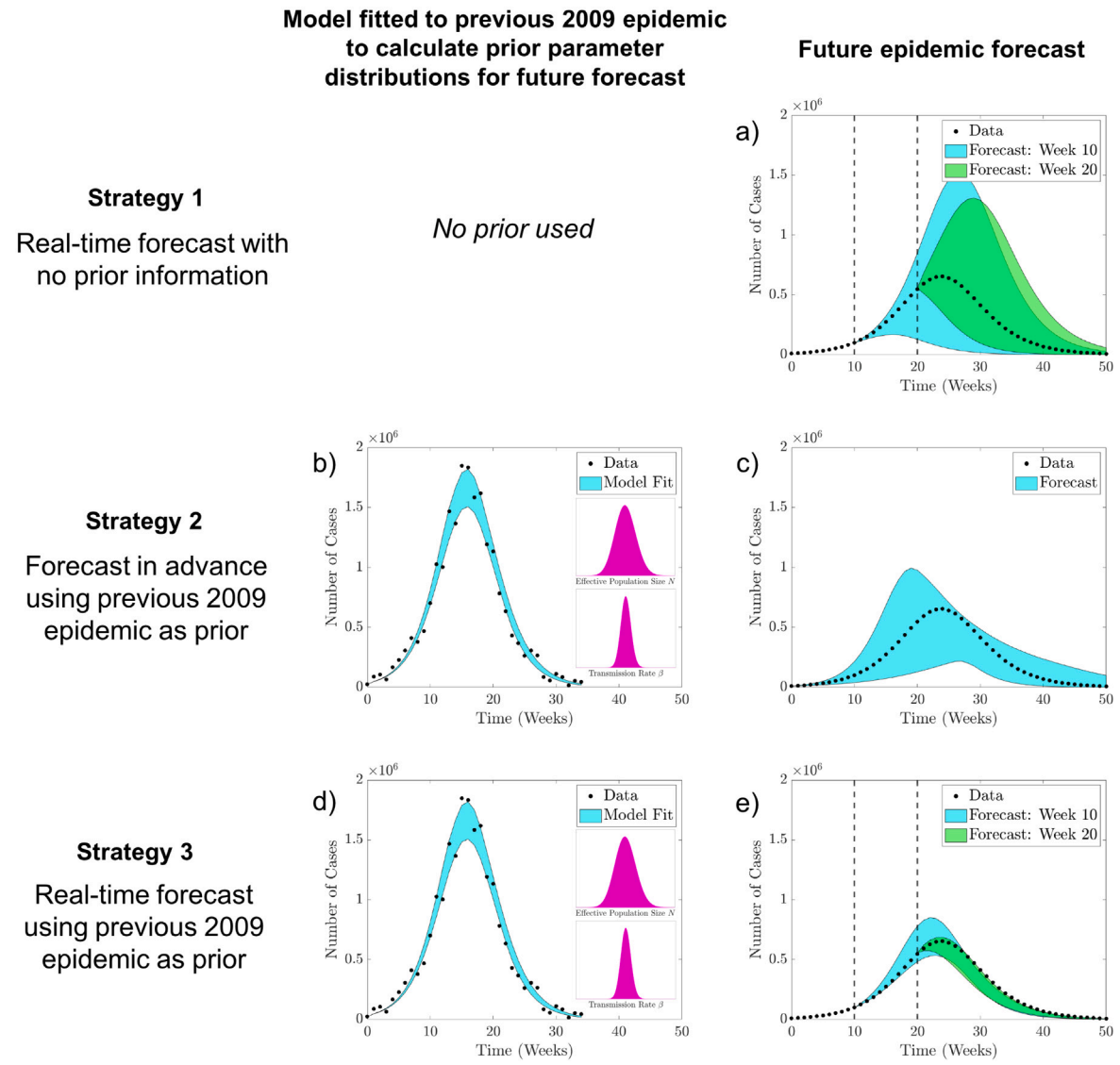


Fig. 2. Schematic illustrating the modelling approaches considered for forecasting the dynamics of a future epidemic. The shaded regions indicate the 95% CrIs of epidemic trajectories and forecasts. (a) Strategy 1: Forecast in real-time, using data from the ongoing epidemic and assuming no prior information about the fitting parameters. Cyan and green forecasts calibrated using data up to week 10 and 20 of the epidemic, respectively. (b)–(c) Strategy 2: Forecast in advance of a future epidemic using prior parameter distributions estimated by fitting the model to data from a previous epidemic (priors are shown as subfigures in (b)). (d)–(e) Strategy 3: Forecast in real-time, using data from the ongoing epidemic as well as prior parameter distributions estimated by fitting the model to data from a previous epidemic (priors are shown as subfigures in (d)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(d)). The mean estimated values of R_0 for the 1-group and 2-group models are 1.644 (95% CrI [1.627, 1.662]) and 1.597 (95% CrI [1.580, 1.612]) respectively, comparable with the interquartile range of 1.30 to 1.70 based on fifty-seven studies of the 2009 H1N1 pandemic strain (Biggerstaff et al., 2014). The values of the estimated parameters and their corresponding 95% CrIs are stated in Table 2. The numbers of recorded, unrecorded, and combined total weekly cases estimated using the 2-group model are shown in Supplementary Information Section S.8.

We used the mean estimated transmission rate and effective population size from the 2-group model to generate synthetic data for future epidemics. We assumed that, if the simulated epidemic takes place further into the future, then the cross-immune fraction of the population is lower due to deaths of cross-immune hosts and births of immunologically naive hosts (see Supplementary Information Section S.7).

Table 2
Mean values and CrIs of the fitting parameter posterior distributions, for the 1-group and 2-group models fitted to data from the 2009 H1N1 influenza epidemic in Japan.

Parameter	Mean	95% CrI
β	1.644	[1.627, 1.662]
N	3.072×10^7	$[2.905, 3.246] \times 10^7$
(a): 1-group model		
Parameter	Mean	95% CrI
β	1.947	[1.927, 1.966]
N	4.660×10^7	$[4.388, 4.938] \times 10^7$
(b): 2-group model		

3.2. Forecasting an epidemic in real-time without prior information

If a major influenza epidemic were to occur, real-time forecasts could be made using live data describing the numbers of cases each week to update predictions. We considered a future epidemic due to a

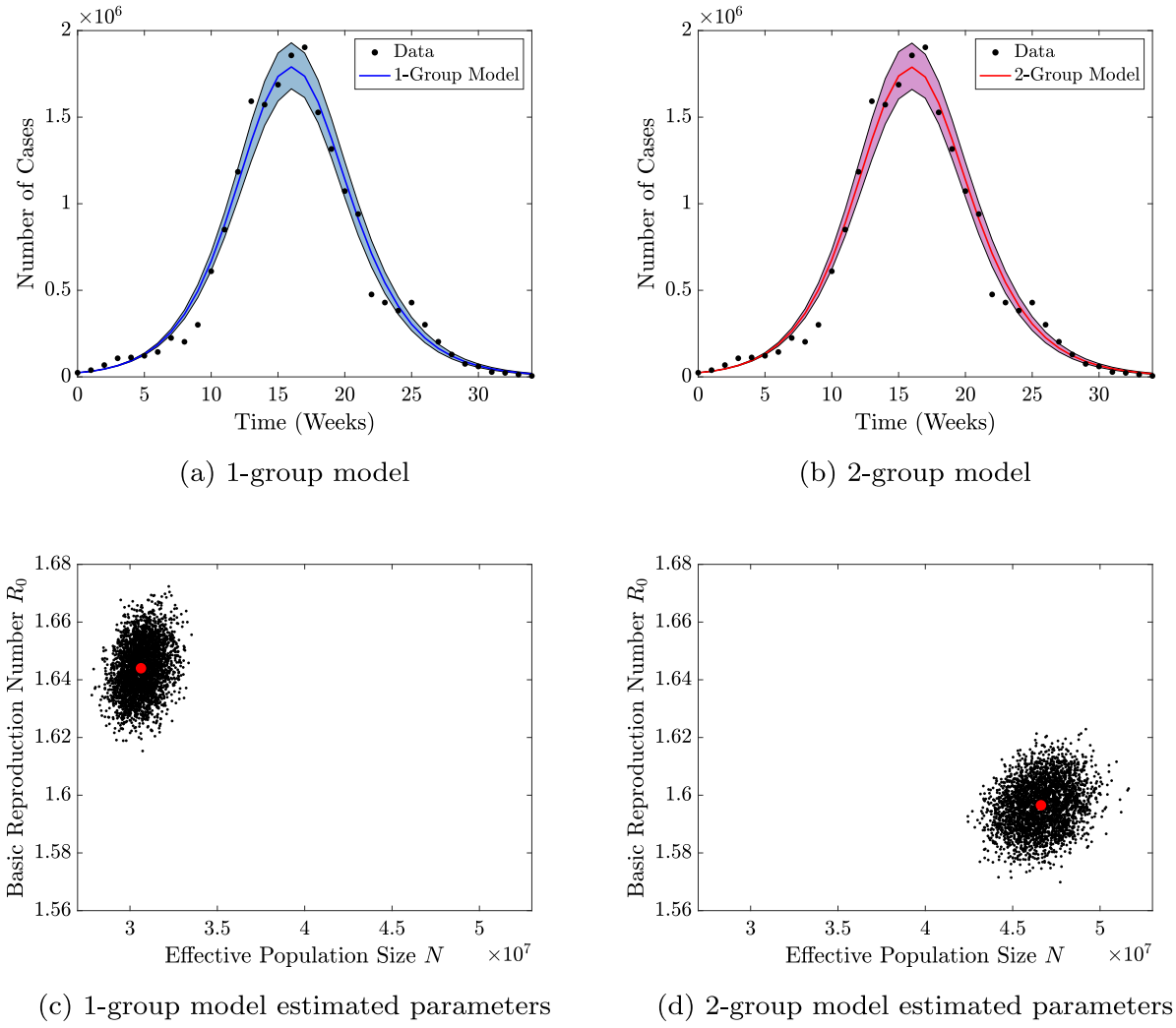


Fig. 3. (a)–(b): The 1-group and 2-group models fitted to data describing the numbers of new recorded cases each week from the 2009 H1N1 influenza epidemic in Japan, using the transmission rate β and effective population size N as fitting parameters. Solid coloured lines and shaded regions indicate the mean and 95% CrIs of epidemic trajectories based on the posterior distributions of the fitted parameters. DIC values are given in Supplementary Information Section S.6. (c)–(d): Scatter plots of the posterior distributions of R_0 (which is directly proportional to β) and N. Red dots represent the mean parameter estimates. Estimated parameters along with their CrIs are given in Table 2.

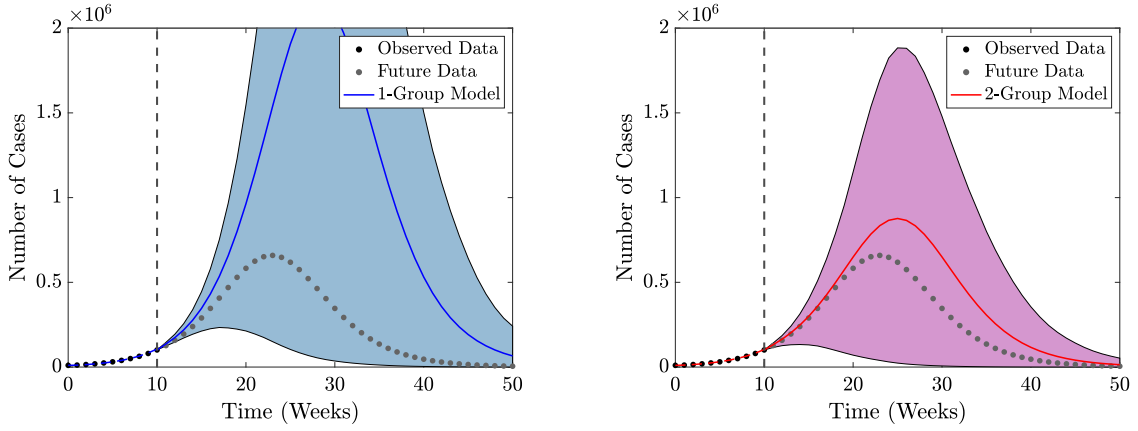
strain that is antigenically similar to the 2009 H1N1 virus occurring 25 years after the 2009 outbreak. We generated forecasts using the 1-group and 2-group models, at 10, 20, and 30 weeks after the first recorded cases. The results presented in Fig. 4 show how the model forecasts change as case notification data become available during the epidemic. The uncertainty in the forecasts of both models is large when predictions are generated early in the epidemic. By contrast, if forecasts are instead generated later, the remainder of the epidemic is predicted accurately. However, for the more accurate predictions obtained in week 30, the peak of the epidemic has already passed, and so accurate forecasting may be less practically useful. We conclude that it is challenging to generate practically useful forecasts of the remainder of an epidemic in real-time without prior information about the parameters governing pathogen transmission. This result motivates us to use information from previous epidemics when forecasting the dynamics of a future one; we investigate this further below.

3.3. Forecasting epidemics in advance

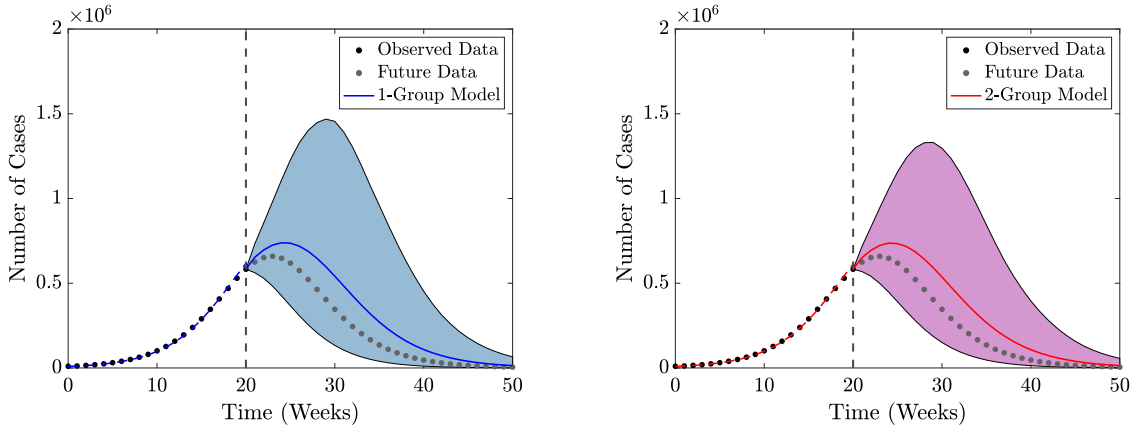
We considered informing forecasts of a future epidemic using gamma distributed estimates of the fitting parameters (β and N). The mean values of these gamma distributions, which were determined from the fit to the 2009 epidemic data, are given in Supplementary Information Section S.9.

We used our models to generate forecasts of the dynamics of future influenza epidemics in Japan due to a related strain and occurring 25, 50, or 75 years after the 2009 epidemic (with no major epidemics occurring in each intervening period). The forecasts in Fig. 5 show that, if the 1-group model is used, the dynamics of a future epidemic are predicted to be identical to those of the 2009 epidemic, regardless of when it occurs. By contrast, for the 2-group model, a large proportion of the population would be cross-immune after the 2009 epidemic, resulting in a lower basic reproduction number. Consequently, if an antigenically related strain were to emerge 25 years later, the epidemic would be smaller than in 2009 (Fig. 5(a)–(b)). If the next major epidemic instead occurred 75 years later, a large proportion of the population would be immunologically naive to a related strain of the 2009 virus (because of population turnover due to births and deaths), resulting in a greater basic reproduction number. Hence, if all other factors were similar to those in 2009, the future epidemic would be larger than in 2009 (Fig. 5(e)–(f)).

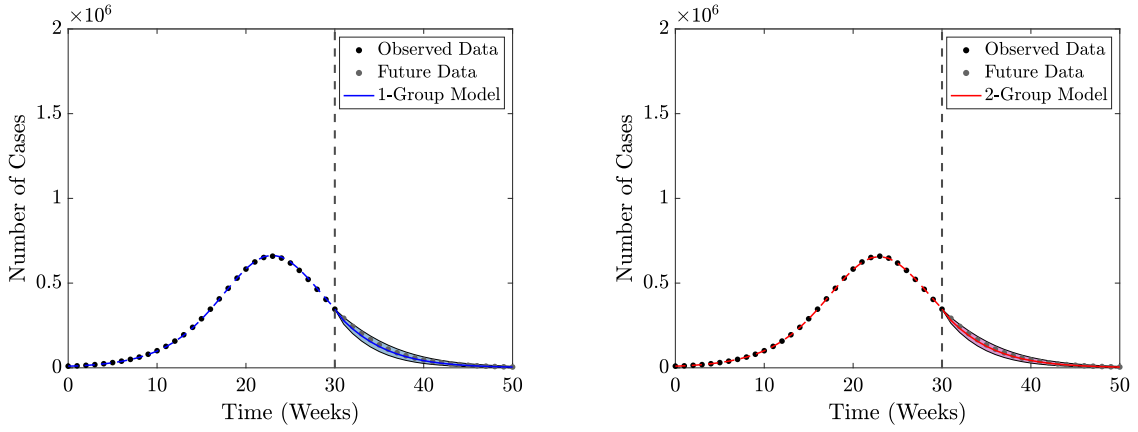
Assuming that the 2-group model reflects the underlying epidemiology more accurately than the 1-group model, we conclude that forecasts generated using the 1-group model may not predict the dynamics of a future epidemic in which cross-immunity is present closely.



(a) 1-group model: week 10 (b) 2-group model: week 10



(c) 1-group model: week 20 (d) 2-group model: week 20



(e) 1-group model: week 30 (f) 2-group model: week 30

Fig. 4. Forecast Strategy 1: Real-time forecasts obtained from the 1-group and 2-group models for a future epidemic occurring 25 years after the 2009 epidemic, calibrated by fitting the model parameters β and N to data describing the weekly numbers of new cases, using uninformative uniform priors. Forecasts were made in weeks 10, 20, and 30 of the epidemic, using the observed data up until those times to estimate model parameters. Dashed vertical lines separate the calibration and forecasting periods. Other dashed lines indicate the mean of the epidemic trajectories in the model calibration period. Solid coloured lines and shaded regions indicate the mean and 95% CrIs of the forecasts, based on the posterior distributions of the parameters. The synthetic data were generated using the mean parameters of the 2-group model fitted to data from the 2009 epidemic. Uniform priors $N \in [10 \times 10^6, 128 \times 10^6]$ and $\beta \in [1, 3]$ were used in the estimation. DIC values are given in Table S1.

Forecasts using larger and smaller variances of the distributions of β and N are presented in Supplementary Information Section S.10. The dependence of a range of quantities obtained using the 2-group model (the cross-immune fraction at the start of the future epidemic, R_0, total number of recorded cases, duration, and size and timing of the epidemic peak) on the time period between the 2009 epidemic and the future epidemic is shown in Supplementary Information Section S.11. As seen in Fig. 5, the further into the future the next epidemic of a related

strain occurs then, all else being equal, the greater the total and peak number of cases and the shorter the duration of the epidemic. This is due to the smaller proportion of cross-immune individuals leading to a higher value of R_0. We note that the impact of R_0 on the peak, final size and duration of an epidemic has been explored previously for simple epidemiological models (Weiss, 2013; Thompson et al., 2020a).

3.4. Forecasting an epidemic in real-time with prior information

As shown above, real-time forecasts generated during a future influenza epidemic, without informative priors for the fitting parameters, can be very uncertain (e.g. Fig. 4(a)–(b)). We therefore also considered using priors to inform the fitted parameter values, so that real-time forecasts are based on both historical data (from the 2009 epidemic) and live data from the ongoing outbreak. Gamma distributed priors were set for β and N, with mean values based on the parameter estimates obtained using the data from the 2009 epidemic.

As before, we considered a scenario in which an epidemic occurs 25 years after the 2009 epidemic. In turn, predictions were made 0, 10, 20, and 30 weeks after the start of the future epidemic (Fig. 6(a)–(b), (c)–(e), (f)–(h) and (i)–(k), respectively).

We considered using priors of different widths to inform the epidemic forecasts (Fig. 6 and Supplementary Information Section S.12). Under the baseline variance considered, when the 1-group model was used, there was sometimes a discrepancy between the calibrated model trajectory and the observed epidemic data (e.g. left part of Fig. 6(f)). For that reason, we also show epidemic forecasts obtained using a wider prior (Fig. 6(d), (g) and (j)), so that the fitted model reflects the observed data more accurately. When the 1-group model was used, forecasts were either inaccurate (when a prior with low variance was used; e.g. Fig. 6(c)) or imprecise (when a prior with higher variance was used; e.g. Fig. 6(d)). In either case, as shown quantitatively by the DIC values in Table S1, our main conclusion is unchanged: predictions improved when forecasts were generated using the more epidemiologically realistic 2-group model.

4. Discussion

Influenza epidemics and pandemics place a significant burden on healthcare systems throughout the world (Monto, 2004). Exposure to an influenza virus confers cross-immunity to antigenically related strains (Kreijtz et al., 2011), however cross-immunity is not frequently included explicitly in influenza forecasting models (Baguelin et al., 2013; Rajaram et al., 2017). In this study, we have investigated whether or not it is necessary to account for cross-immunity when generating forecasts during influenza epidemics and, moreover, whether data from previous epidemics can be used to improve forecast accuracy.

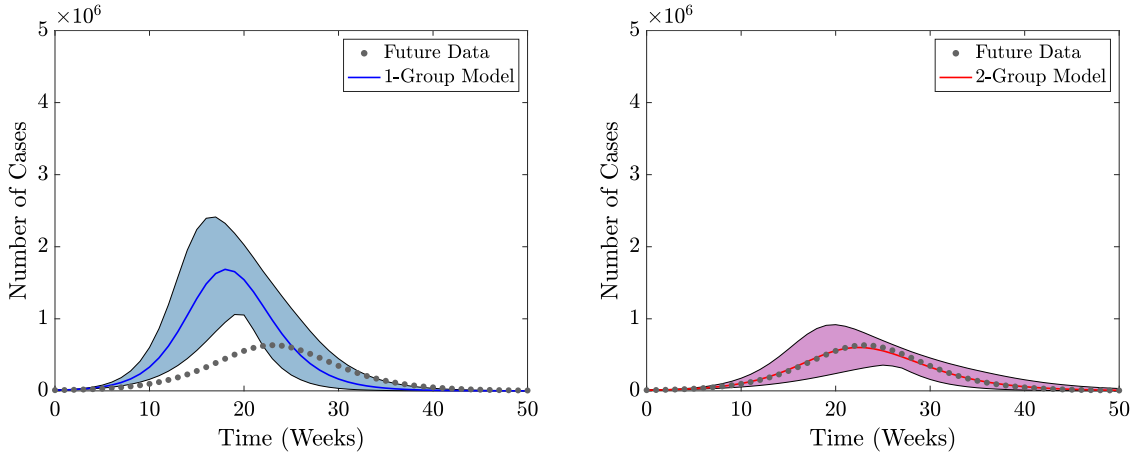
We have considered two different mathematical models that describe pathogen transmission: a 2-group model in which immunologically naive and cross-immune individuals are differentiated between and a 1-group model in which all individuals are assumed to have similar characteristics. We parameterised each model using data describing the estimated numbers of infected individuals seeking medical attention per week in Japan during the 2009 H1N1 influenza pandemic (Nishiura, 2011; Omori and Nishiura, 2011). We then considered a scenario in which we predict the dynamics of an epidemic of an antigenically related strain occurring 25 years after the 2009 pandemic. When no prior knowledge about the values of the transmission rate and effective population size is assumed, neither model can predict future epidemiological dynamics in real-time early in the epidemic with any certainty. Previous research has also indicated that significant uncertainty exists when ordinary differential equation models are used to generate real-time forecasts early in influenza epidemics (Hall et al., 2007).

We then considered the effect of the time period between epidemics on the accuracy of epidemic forecasts made in advance of the future epidemic. Immediately after the 2009 epidemic, a large fraction of the population will have been cross-immune to strains that are related to the 2009 H1N1 virus. This fraction reduces as the time since the 2009 epidemic increases, as individuals (a large proportion of whom may have acquired cross-immunity) die and immunologically naive individuals are born. Consequently, the expected size of a future epidemic of a related strain increases the further into the future at which it occurs. If we neglect cross-immunity by using the 1-group model, we predict the same epidemic dynamics as in 2009, regardless of when the future epidemic occurs. This is because changing numbers of cross-immune individuals are not accounted for in that model. This could result in overestimation of the size of a future epidemic, if the cross-immune fraction was greater than the baseline cross-immunity in 2009 (i.e. if the future epidemic occurred soon after 2009), or underestimation of the epidemic size if the cross-immune fraction was lower than in 2009 (i.e. if the future epidemic occurred long after 2009).

Finally, we considered incorporating knowledge of parameters from the 2009 epidemic, in combination with case notification data obtained in real-time during the future epidemic, to update forecasts as the future epidemic is ongoing. When the 1-group model was used to make forecasts, we found that priors with significant uncertainty had to be used to calibrate the model trajectories to the data. Although these priors, set based on the model fits to the 2009 epidemic data, led to improved forecasts compared to when no prior information was used, the forecasts were still inaccurate or uncertain when made before the peak of the epidemic. By contrast, the 2-group model was able to generate more accurate forecasts. This is because cross-immunity is accounted for in the 2-group model, and the priors reflect the values of the true underlying parameters more accurately. We conclude that, to forecast the long-term dynamics of major influenza epidemics caused by strains that are antigenically related to those responsible for previous epidemics, a model that accounts for cross-immunity should be used, and data obtained during previous epidemics should be taken into account. Additionally, we note that short-term forecasts on the order of one to four weeks – a time horizon used by the US Centers for Disease Control when constructing seasonal influenza forecasts (Biggerstaff et al., 2016, 2018; Centers for Disease Control and Prevention (CDC), 2020) – are also more accurate when generated using the 2-group model (see Fig. 6).

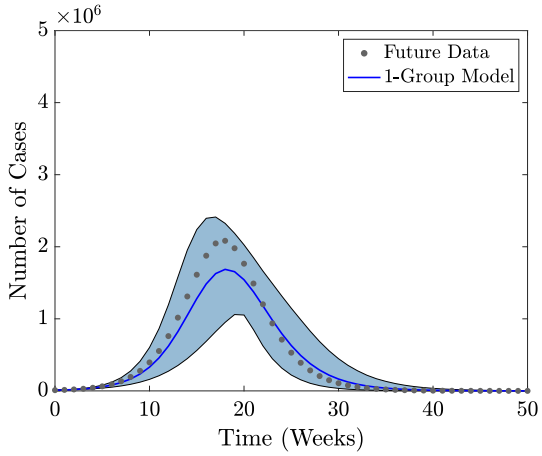
We note that there may be instances in which the underlying epidemiology of an outbreak is not well-known, or where a complex model cannot be parameterised due to ineffective surveillance or limited data availability (Gibbons et al., 2014; Thompson et al., 2020d). In such cases, using a simple model akin to the 1-group model used in this study may be the only possible option for making predictions. Although forecasts made using a simple model may lack precision, they could still be useful to policy makers during an epidemic. For example, the 1-group model was able to predict the duration of the epidemic accurately when using data from the first 10 weeks of the outbreak, even if it could not predict the trajectory of the entire epidemic perfectly. Simple models may be particularly useful for short-term forecasts (Funk et al., 2019). By constantly updating model predictions using newly acquired data, and refining the modelling framework when it is unable to replicate observed data, simple models that do not describe the underlying epidemiology of an epidemic fully may still provide useful insights.

We investigated whether or not it is necessary to include a particular source of heterogeneity (i.e. cross-immunity) when constructing influenza epidemic forecasts. Our analysis used case notification data from Japan collected during the 2009 influenza pandemic. Although the exact dataset underlying our analysis was not central to our main conclusion, it would be possible to replicate our study using any number of other influenza datasets (Donaldson et al., 2009; Pourbohloul et al., 2009; Earn, 2012; National Institute of Infectious Diseases, 2020). Going forwards, we could also consider how accounting for cross-immunity would affect forecasts of seasonal epidemics, in which case

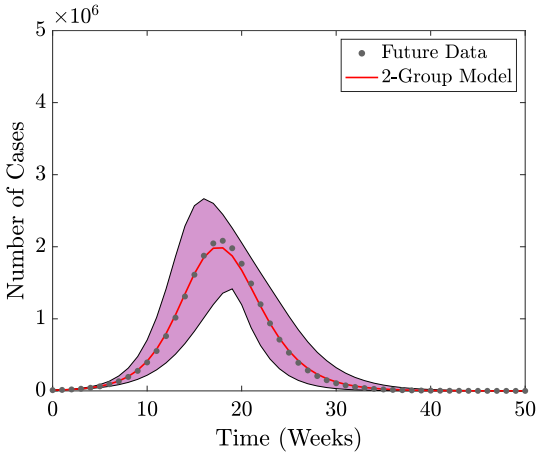


(a) 1-group model: 25 years later

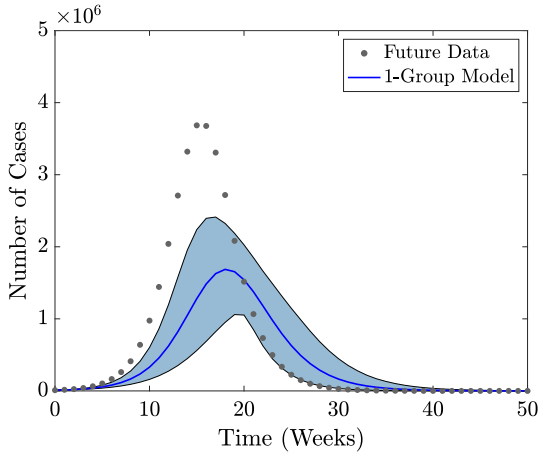
(b) 2-group model: 25 years later



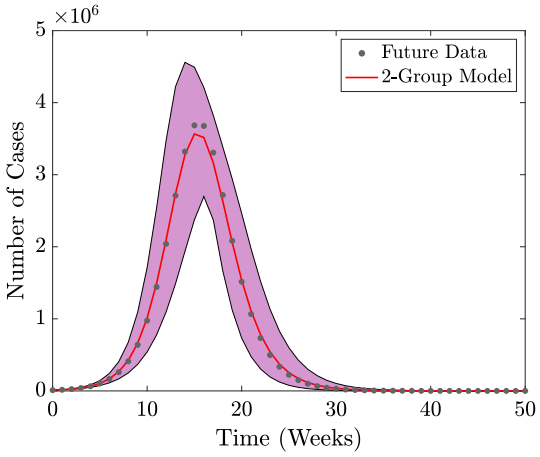
(c) 1-group model: 50 years later



(d) 2-group model: 50 years later

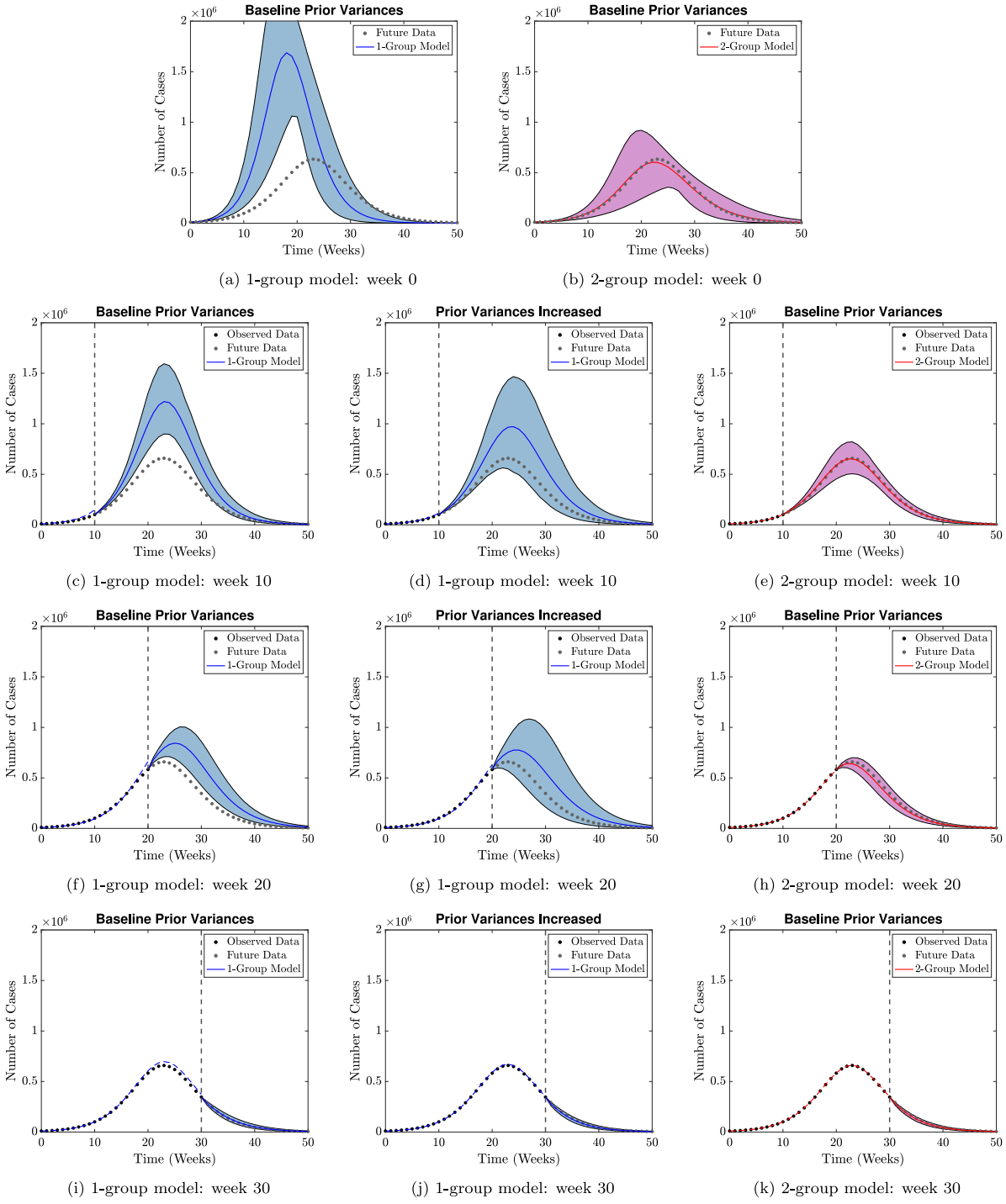


(e) 1-group model: 75 years later



(f) 2-group model: 75 years later

Fig. 5. Forecast Strategy 2: Forecasts obtained at the start of future epidemics using the 1-group and 2-group models, for epidemics occurring 25, 50, and 75 years after the 2009 epidemic. Forecasts were generated by assuming that the parameters β and N follow a gamma distribution, the parameters of which were determined by fitting the models to data from the previous 2009 epidemic (Supplementary Information Section S.9). Solid coloured lines and shaded regions indicate the mean and 95% CrIs of the forecasts. The synthetic data were generated using the mean parameters of the 2-group model fitted to data from the 2009 epidemic. DIC values are given in Table S1.



(a) 1-group model: week 0 (b) 2-group model: week 0

(c) 1-group model: week 10 (d) 1-group model: week 10 (e) 2-group model: week 10

(f) 1-group model: week 20 (g) 1-group model: week 20 (h) 2-group model: week 20

(i) 1-group model: week 30 (j) 1-group model: week 30 (k) 2-group model: week 30

Fig. 6. Forecast Strategy 3: Forecasts obtained using the 1-group and 2-group models during a future epidemic occurring 25 years after the 2009 epidemic, at the start of the epidemic ((a)–(b)), and using case notification data obtained in real-time during the epidemic ((c)–(k)). Gamma distributed priors are prescribed for the fitting parameters β and N, the parameters of which were determined by fitting the models to data from the previous 2009 epidemic (Supplementary Information Section S.9). Forecasts are generated in weeks 10, 20, and 30 of the epidemic, using the observed data up until those times to estimate model parameters. Dashed vertical lines separate the calibration and forecasting periods. Other dashed lines indicate the mean of the epidemic trajectories in the model calibration period. Solid coloured lines and shaded regions indicate the mean and 95% CrIs of the forecasts, based on the posterior distributions of the parameters. The synthetic data were generated using the mean parameters of the 2-group model fitted to data from the 2009 epidemic. DIC values are given in Table S1.

the particular strains driving dynamics in different seasons would need to be considered (Petrova and Russell, 2017). Consideration of whether and how forecasts of epidemics of pandemic influenza may be influenced by circulating seasonal strains (Fox et al., 2017) is a target for future work. We could extend our models to investigate whether or not other sources of heterogeneity should be accounted for. For instance, age-structure could be incorporated, taking into account the effects of immune imprinting (Gostic et al., 2016, 2019). Additionally, we could include spatial heterogeneity by partitioning the population into distinct geographical regions or introducing a contact network structure (Meyers et al., 2006; Volz and Meyers, 2007; Ohkusa et al., 2009; Volz et al., 2011; Miller and Kiss, 2014). Another potential avenue for further investigation may be to incorporate transmission models that account for cross-immunity into a phylodynamic framework to

predict which strains of influenza may emerge and the dynamics of their respective epidemics (Grenfell, 2004).

In this study, we have considered the simple example of binary immunity (i.e. a class of cross-immune individuals and a class of immunologically naive individuals were included). In reality, the landscape of immunity within a population is much more complex, with individuals exhibiting varying levels of immunity based on their lifetime history of exposure to influenza viruses (Laurie et al., 2010; Gostic et al., 2016, 2019) and their age (Lambert et al., 2012; Haq and McElhaney, 2014). Underlying health conditions such as obesity and heart disease may also impact individuals' immune responses (Hui et al., 2006; Honce and Schultz-Cherry, 2019). Nonetheless, even the simple framework that we considered allowed us to show that cross-immunity should be accounted for when making influenza epidemic forecasts. Future work could involve models containing numerous classes to account for population heterogeneities or detailed infection dynamics (Thompson and Hart, 2018; Hart et al., 2020), or even a continuum level of immunity within the population based on the above-mentioned factors (Andreasen et al., 1997; Martcheva and Pilyugin, 2006).

In the 2-group model considered here, we assumed, as in Reichert et al. (2012), that immunoprotection does not prevent infection, but instead alters its consequences. Different types of cross-immunity to related strains of a virus can be considered. For example, cross-immunity could instead be assumed to reduce an individual's susceptibility to infection (Hill et al., 2019; Thompson et al., 2019). Future work could consider whether or not the results of this study hold when different assumptions are made about the precise effects of cross-immunity. In the 2-group model, in order to study the effects of cross-immunity in as simple a setting as possible, we assumed that infected individuals who did not seek medical attention had cross-immune protection against the virus. However, a range of factors (including age and behaviour) affect whether or not, and how quickly, an individual seeks medical attention (Thompson, 2020c). This could be built into the underlying modelling framework considered here, although additional data would be needed to parameterise the resulting model. Other additions to the 1- and 2-group models could also be considered. For example, the wide range of interventions that are implemented during outbreaks could be included in the models explicitly (Gani et al., 2005; Longini Jr. et al., 2005; Backer et al., 2019).

Despite its simplicity, our approach has enabled us to demonstrate that including cross-immunity in influenza epidemic forecasting models can lead to more accurate forecasts. Cross-immunity due to previous infections has been shown to play a major role in the dynamics of influenza epidemics, with clear evidence emerging from analyses of data from the 1918 Spanish Flu pandemic (Taubenberger and Morens, 2006) and the 2009 H1N1 influenza pandemic (Hancock et al., 2009). Cross-immunity will contribute to shaping the dynamics of future influenza epidemics. Consideration of cross-immunity by epidemiological modellers is therefore of obvious public health importance.

Funding

This publication is based on work supported by the EPSRC, UK Centre for Doctoral Training in Industrially Focused Mathematical Modelling (EP/L015803/1) in collaboration with Biosensors Beyond Borders Ltd. (RS-P). It was also funded by Christ Church (Oxford), UK via a Junior Research Fellowship (RNT).

CRediT authorship contribution statement

Rahil Sachak-Patwa: Conceived the study, Conducted the analysis, Writing - review & editing. **Helen M. Byrne:** Conceived the study, Supervised the research, Writing - review & editing. **Robin N. Thompson:** Conceived the study, Supervised the research, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Thanks to Erin I Lafferty and Claude J Schmit (Biosensors Beyond Borders Ltd.), Craig P Thompson (University of Oxford), and members of the Wolfson Centre for Mathematical Biology (University of Oxford) for helpful discussions about this research.

Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.epidem.2020.100432.

References

Anderson, R.M., May, R.M., 1991. Infectious Diseases of Humans: Dynamics and Control. Oxford University Press.

Andreasen, V., Lin, J., Levin, S.A., 1997. The dynamics of cocirculating influenza strains conferring partial cross-immunity. J. Math. Biol. 35 (7), 825–842. http://dx.doi.org/10.1007/s002850050079.

Backer, J., Wallinga, J., Meijer, A., Donker, G., Van der Hoek, W., Van Boven, M., 2019. The impact of influenza vaccination on infection, hospitalisation and mortality in the Netherlands between 2003 and 2015. Epidemics 26, 77–85. http://dx.doi.org/10.1016/j.epidem.2018.10.001.

Baguelin, M., Flasche, S., Camacho, A., Demiris, N., Miller, E., Edmunds, W.J., 2013. Assessing optimal target populations for influenza vaccination programmes: an evidence synthesis and modelling study. PLoS Med. 10 (10), e1001527. http://dx.doi.org/10.1371/journal.pmed.1001527.

Bandaranayake, D., Huang, Q.S., Bissielo, A., Wood, T., Mackereth, G., Baker, M.G., et al., 2010. Risk factors and immunity in a nationally representative population following the 2009 influenza A(H1N1) pandemic. PLoS One 5 (10), e13211. http://dx.doi.org/10.1371/journal.pone.0013211.

Bettencourt, L.M., Ribeiro, R.M., 2008. Real time bayesian estimation of the epidemic potential of emerging infectious diseases. PLoS One 3 (5), e2185. http://dx.doi.org/10.1371/journal.pone.0002185.

Biggerstaff, M., Alper, D., Dredze, M., Fox, S., Fung, I.C.-H., Hickmann, K.S., et al., 2016. Results from the centers for disease control and prevention's predict the 2013–2014 Influenza Season Challenge. BMC Infect. Dis. 16 (1), http://dx.doi.org/10.1186/s12879-016-1669-x.

Biggerstaff, M., Cauchemez, S., Reed, C., Gambhir, M., Finelli, L., 2014. Estimates of the reproduction number for seasonal, pandemic, and zoonotic influenza: a systematic review of the literature. BMC Infect. Dis. 14 (1), http://dx.doi.org/10.1186/1471-2334-14-480.

Biggerstaff, M., Johansson, M., Alper, D., Brooks, L.C., Chakraborty, P., Farrow, D.C., et al., 2018. Results from the second year of a collaborative effort to forecast influenza seasons in the United States. Epidemics 24, 26–33. http://dx.doi.org/10.1016/j.epidem.2018.02.003.

Bouvier, N.M., Palese, P., 2008. The biology of influenza viruses. Vaccine 26, D49–D53. http://dx.doi.org/10.1016/j.vaccine.2008.07.039.

Centers for Disease Control and Prevention (CDC), 2020. How CDC uses flu forecasting. https://www.cdc.gov/flu/weekly/flusight/how-flu-forecasting.htm. (Accessed 27 October 2020).

Chen, M.I.C., 2010. 2009 influenza A(H1N1) seroconversion rates and risk factors among distinct adult cohorts in Singapore. JAMA 303 (14), 1383. http://dx.doi.org/10.1001/jama.2010.404.

Chen, S.-C., Liao, C.-M., 2008. Modelling control measures to reduce the impact of pandemic influenza among schoolchildren. Epidemiol. Infect. 136 (8), 1035–1045. http://dx.doi.org/10.1017/S0950268807009284.

Chowell, G., Nishiura, H., Bettencourt, L.M., 2006. Comparative estimation of the reproduction number for pandemic influenza from daily case notification data. J. R. Soc. Interface 4 (12), 155–166. http://dx.doi.org/10.1098/rsif.2006.0161.

Chowell, G., Viboud, C., Wang, X., Bertozzi, S.M., Miller, M.A., 2009. Adaptive vaccination strategies to mitigate pandemic influenza: Mexico as a case study. PLoS One 4 (12), e8164. http://dx.doi.org/10.1371/journal.pone.0008164.

Christman, M.C., Kedwaii, A., Xu, J., Donis, R.O., Lu, G., 2011. Pandemic (H1N1) 2009 virus revisited: an evolutionary retrospective. Infect. Genet. Evol. 11 (5), 803–811. http://dx.doi.org/10.1016/j.meegid.2011.02.021.

Cintrón-Arias, A., Castillo-Chávez, C., Bettencourt, L.M., Lloyd, A.L., Banks, H., 2009. The estimation of the effective reproductive number from disease outbreak data. Math. Biosci. Eng. 6 (2), 261–282. http://dx.doi.org/10.3934/mbe.2009.6.261.

Couch, R.B., Kasel, J.A., Gerin, J.L., Schulman, J.L., Kilbourne, E.D., 1974. Induction of partial immunity to influenza by a neuraminidase-specific vaccine. J. Infect. Dis. 129 (4), 411–420. http://dx.doi.org/10.1093/infdis/129.4.411.

Davies, N.G., Kucharski, A.J., Eggo, R.M., Gimma, A., Edmunds, W.J., Jombart, T., et al., 2020. Effects of non-pharmaceutical interventions on COVID-19 cases, deaths, and demand for hospital services in the UK: a modelling study. Lancet Public Health 5 (7), e375–e385. http://dx.doi.org/10.1016/s2468-2667(20)30133-x.

Donaldson, L.J., Rutter, P.D., Ellis, B.M., Greaves, F.E.C., Mytton, O.T., Pebody, R.G., Yardley, I.E., 2009. Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study. BMJ 339 (dec10 1), b5213. http://dx.doi.org/10.1136/bmj.b5213.

Du, X., King, A.A., Woods, R.J., Pascual, M., 2017. Evolution-informed forecasting of seasonal influenza A (H3N2). Sci. Transl. Med. 9 (413), eaan5325. http://dx.doi.org/10.1126/scitranslmed.aan5325.

Dushoff, J., Plotkin, J.B., Viboud, C., Simonsen, L., Miller, M., Loeb, M., David, J., 2007. Vaccinating to protect a vulnerable subpopulation. PLoS Med. 4 (5), e174. http://dx.doi.org/10.1371/journal.pmed.0040174.

Earn, D.J., 2012. Effects of school closure on incidence of pandemic influenza in Alberta, Canada. Ann. Intern. Med. 156 (3), 173. http://dx.doi.org/10.7326/0003-4819-156-3-201202070-00005.

Ellebedy, A., Ducatez, M., Duan, S., Stigger-Rosser, E., Rubrum, A., Govorkova, E., et al., 2011. Impact of prior seasonal influenza vaccination and infection on pandemic A (H1N1) influenza virus replication in ferrets. Vaccine 29 (17), 3335–3339. http://dx.doi.org/10.1016/j.vaccine.2010.08.067.

Ellebedy, A.H., Fabrizio, T.P., Kayali, G., Oguin, T.H., Brown, S.A., Rehg, J., et al., 2010. Contemporary seasonal influenza A (H1N1) virus infection primes for a more robust response to split inactivated pandemic influenza A (H1N1) virus vaccination in ferrets. Clin. Vaccine Immunol. 17 (12), 1998–2006. http://dx.doi.org/10.1128/cvi.00247-10.

Epstein, S., Misplon, J., Lawson, C., Subbarao, E., Connors, M., Murphy, B., 1993. Beta 2-microglobulin-deficient mice can be protected against influenza A infection by vaccination with vaccinia-influenza recombinants expressing hemagglutinin and neuraminidase.. J. Immunol. 150 (12), 5484–5493.

Fang, Y., Banner, D., Kelvin, A.A., Huang, S.S.H., Paige, C.J., Corfe, S.A., et al., 2011. Seasonal H1N1 influenza virus infection induces cross-protective pandemic H1N1 virus immunity through a CD8-independent, B cell-dependent mechanism. J. Virol. 86 (4), 2229–2238. http://dx.doi.org/10.1128/jvi.05540-11.

Ferguson, N.M., Cummings, D.A., Fraser, C., Cajka, J.C., Cooley, P.C., Burke, D.S., 2006. Strategies for mitigating an influenza pandemic. Nature 442 (7101), 448. http://dx.doi.org/10.1038/nature04795.

Fielding, J.E., Kelly, H.A., Mercer, G.N., Glass, K., 2013. Systematic review of influenza A(H1N1)pdm09 virus shedding: duration is affected by severity, but not age. Influenza Other Respir. Viruses 8 (2), 142–150. http://dx.doi.org/10.1111/irv.12216.

Fox, S.J., Miller, J.C., Meyers, L.A., 2017. Seasonality in risk of pandemic influenza emergence. PLoS Comput. Biol. 13 (10), e1005749. http://dx.doi.org/10.1371/journal.pcbi.1005749.

Fraser, C., Donnelly, C.A., Cauchemez, S., Hanage, W.P., Van Kerkhove, M.D., Hollingsworth, T.D., et al., 2009. Pandemic potential of a strain of influenza A (H1N1): early findings. Science 324 (5934), 1557–1561. http://dx.doi.org/10.1126/science.1176062.

Frost, S.D., Pybus, O.G., Gog, J.R., Viboud, C., Bonhoeffer, S., Bedford, T., 2015. Eight challenges in phylodynamic inference. Epidemics 10, 88–92. http://dx.doi.org/10.1016/j.epidem.2014.09.001.

Funk, S., Camacho, A., Kucharski, A.J., Lowe, R., Eggo, R.M., Edmunds, W.J., 2019. Assessing the performance of real-time epidemic forecasts: A case study of Ebola in the Western Area region of Sierra Leone, 2014–15. PLoS Comput. Biol. 15 (2), e1006785. http://dx.doi.org/10.1371/journal.pcbi.1006785.

Gani, R., Hughes, H., Fleming, D., Griffin, T., Medlock, J., Leach, S., 2005. Potential impact of antiviral drug use during influenza pandemic. Emerg. Infect. Diseases 11 (9), 1355. http://dx.doi.org/10.3201/eid1109.041344.

Gart, J.J., 1968. The mathematical analysis of an epidemic with two kinds of susceptibles. Biometrics 24 (3), 557. http://dx.doi.org/10.2307/2528318.

Gibbons, C.L., Mangen, M.-J.J., Plass, D., Havelaar, A.H., Brooke, R.J., Kramarz, P., et al., 2014. Measuring underreporting and under-ascertainment in infectious disease datasets: a comparison of methods. BMC Public Health 14 (1), 147. http://dx.doi.org/10.1186/1471-2458-14-147.

Glasser, J., Taneri, D., Feng, Z., Chuang, J.-H., Tüll, P., Thompson, W., et al., 2010. Evaluation of targeted influenza vaccination strategies via population modeling. PLoS One 5 (9), e12777. http://dx.doi.org/10.1371/journal.pone.0012777.

Gostic, K.M., Ambrose, M., Worobey, M., Lloyd-Smith, J.O., 2016. Potent protection against H5N1 and H7N9 influenza via childhood hemagglutinin imprinting. Science 354 (6313), 722–726. http://dx.doi.org/10.1126/science.aag1322.

Gostic, K.M., Bridge, R., Brady, S., Viboud, C., Worobey, M., Lloyd-Smith, J.O., 2019. Childhood immune imprinting to influenza A shapes birth year-specific risk during seasonal H1N1 and H3N2 epidemics. PLoS Pathog. 15 (12), http://dx.doi.org/10.1371/journal.ppat.1008109.

Grebe, K.M., Yewdell, J.W., Bennink, J.R., 2008. Heterosubtypic immunity to influenza A virus: where do we stand? Microb. Infect. 10 (9), 1024–1029. http://dx.doi.org/10.1016/j.micinf.2008.07.002.

Grenfell, B.T., 2004. Unifying the epidemiological and evolutionary dynamics of pathogens. Science 303 (5656), 327–332. http://dx.doi.org/10.1126/science.1090727.

Hall, I.M., Gani, R., Hughes, H.E., Leach, S., 2007. Real-time epidemic forecasting for pandemic influenza. Epidemiol. Infect. 135 (3), 372–385. http://dx.doi.org/10.1017/s0950268806007084.

Hancock, K., Veguilla, V., Lu, X., Zhong, W., Butler, E.N., Sun, H., et al., 2009. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. N. Engl. J. Med. 361 (20), 1945–1952. http://dx.doi.org/10.1056/NEJMoa0906453.

Haq, K., McElhaney, J.E., 2014. Immunosenescence: influenza vaccination and the elderly. Curr. Opin. Immunol. 29, 38–42. http://dx.doi.org/10.1016/j.coi.2014.03.008.

Hardelid, P., Andrews, N., Hoschler, K., Stanford, E., Baguelin, M., Waight, P., et al., 2010. Assessment of baseline age-specific antibody prevalence and incidence of infection to novel influenza A/H1N1 2009. Health Technol. Assess. 14 (55), 115–192. http://dx.doi.org/10.3310/hta14550-03.

Hart, W.S., Maini, P.K., Yates, C.A., Thompson, R.N., 2020. A theoretical framework for transitioning from patient-level to population-scale epidemiological dynamics: influenza A as a case study. J. R. Soc. Interface 17 (166), 20200230. http://dx.doi.org/10.1098/rsif.2020.0230.

Hastings, W.K., 1970. Monte Carlo sampling methods using Markov chains and their applications. Biometrika 57 (1), 97–109. http://dx.doi.org/10.1093/biomet/57.1.97.

He, D., Lui, R., Wang, L., Tse, C.K., Yang, L., Stone, L., 2015. Global spatio-temporal patterns of influenza in the post-pandemic era. Sci. Rep. 5 (1), http://dx.doi.org/10.1038/srep11013.

Hill, E.M., Petrou, S., de Lusignan, S., Yonova, I., Keeling, M.J., 2019. Seasonal influenza: Modelling approaches to capture immunity propagation. PLoS Comput. Biol. 15 (10), 1–26. http://dx.doi.org/10.1371/journal.pcbi.1007096.

Honce, R., Schultz-Cherry, S., 2019. Impact of obesity on influenza A virus pathogenesis, immune response, and evolution. Front. Immunol. 10, http://dx.doi.org/10.3389/fimmu.2019.01071.

Huang, S.S.H., Lin, Z., Banner, D., León, A.J., Paquette, S.G., Rubin, B., et al., 2013. Immunity toward H1N1 influenza hemagglutinin of historical and contemporary strains suggests protection and vaccine failure. Sci. Rep. 3 (1), http://dx.doi.org/10.1038/srep01698.

Hui, S., Chu, L., Peiris, J., Chan, K., Chu, D., Tsui, W., 2006. Immune response to influenza vaccination in community-dwelling Chinese elderly persons. Vaccine 24 (25), 5371–5380. http://dx.doi.org/10.1016/j.vaccine.2006.04.032.

Johnson, N.P., Mueller, J., 2002. Updating the accounts: global mortality of the 1918–1920 "Spanish" influenza pandemic. Bull. Hist. Med. 76 (1), 105–115. http://dx.doi.org/10.1353/bhm.2002.0022.

Kamigaki, T., Oshitani, H., 2009. Epidemiological characteristics and low case fatality rate of pandemic (H1N1) 2009 in Japan. PLoS Curr. 1, RRN1139. http://dx.doi.org/10.1371/currents.rrn1139.

Kash, J.C., Qi, L., Dugan, V.G., Jagger, B.W., Hrabal, R.J., Memoli, M.J., et al., 2010. Prior infection with classical swine H1N1 influenza viruses is associated with protective immunity to the 2009 pandemic H1N1 virus. Influenza Other Respir. Viruses 4 (3), 121–127. http://dx.doi.org/10.1111/j.1750-2659.2010.00132.x.

Kelly, H., Peck, H.A., Laurie, K.L., Wu, P., Nishiura, H., Cowling, B.J., 2011. The age-specific cumulative incidence of infection with pandemic influenza H1N1 2009 was similar in various countries prior to vaccination. PLoS One 6 (8), e21828. http://dx.doi.org/10.1371/journal.pone.0021828.

Kilbourne, E.D., 2006. Influenza pandemics of the 20th century. Emerg. Infect. Diseases 12 (1), 9–14. http://dx.doi.org/10.3201/eid1201.051254.

Kim, H., Webster, R.G., Webby, R.J., 2018. Influenza virus: dealing with a drifting and shifting pathogen. Viral Immunol. 31 (2), 174–183. http://dx.doi.org/10.1089/vim.2017.0141.

Klepac, P., Kissler, S., Gog, J., 2018. Contagion! The BBC Four Pandemic–The model behind the documentary. Epidemics 24, 49–59. http://dx.doi.org/10.1016/j.epidem.2018.03.003.

Koelle, K., Cobey, S., Grenfell, B., Pascual, M., 2006. Epochal evolution shapes the phylodynamics of interpandemic influenza a (H3N2) in humans. Science 314 (5807), 1898–1903. http://dx.doi.org/10.1126/science.1132745.

Krammer, F., 2019. The human antibody response to influenza a virus infection and vaccination. Nat. Rev. Immunol. 19 (6), 383–397. http://dx.doi.org/10.1038/s41577-019-0143-6.

Kreijtz, J., Fouchier, R., Rimmelzwaan, G., 2011. Immune responses to influenza virus infection. Virus Res. 162 (1–2), 19–30. http://dx.doi.org/10.1016/j.virusres.2011.09.022.

Lambert, N.D., Ovsyannikova, I.G., Pankratz, V.S., Jacobson, R.M., Poland, G.A., 2012. Understanding the immune response to seasonal influenza vaccination in older adults: a systems biology approach. Expert Rev. Vaccines 11 (8), 985–994. http://dx.doi.org/10.1586/erv.12.61.

Laurie, K.L., Carolan, L.A., Middleton, D., Lowther, S., Kelso, A., Barr, I.G., 2010. Multiple infections with seasonal influenza a virus induce cross-protective immunity against A(H1N1) pandemic influenza virus in a ferret model. J. Infect. Dis. 202 (7), 1011–1020. http://dx.doi.org/10.1086/656188.

Longini Jr., I.M., Halloran, M.E., Nizam, A., Yang, Y., 2004. Containing pandemic influenza with antiviral agents. Am. J. Epidemiol. 159 (7), 623–633. http://dx.doi.org/10.1093/aje/kwh092.

Longini Jr., I.M., Nizam, A., Xu, S., Ungchusak, K., Hanshaoworakul, W., Cummings, D.A., Halloran, M.E., 2005. Containing pandemic influenza at the source. Science 309 (5737), 1083–1087. http://dx.doi.org/10.1126/science.1115717.

Martcheva, M., Pilyugin, S.S., 2006. An epidemic model structured by host immunity. J. Biol. Syst. 14 (02), 185–203. http://dx.doi.org/10.1142/s0218339006001787.

Medlock, J., Galvani, A.P., 2009. Optimizing influenza vaccine distribution. Science 325 (5948), 1705–1708. http://dx.doi.org/10.1126/science.1175570.

Meyers, L.A., Newman, M., Pourbohloul, B., 2006. Predicting epidemics on directed contact networks. J. Theoret. Biol. 240 (3), 400–418. http://dx.doi.org/10.1016/j.jtbi.2005.10.004.

Miller, E., Hoschler, K., Hardelid, P., Stanford, E., Andrews, N., Zambon, M., 2010. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. Lancet 375 (9720), 1100–1108. http://dx.doi.org/10.1016/s0140-6736(09)62126-7.

Miller, J.C., Kiss, I.Z., 2014. Epidemic spread in networks: Existing methods and current challenges. Math. Model. Nat. Phenom. 9 (2), 4–42. http://dx.doi.org/10.1051/mmnp/20149202.

Mills, C.E., Robins, J.M., Lipsitch, M., 2004. Transmissibility of 1918 pandemic influenza. Nature 432 (7019), 904–906. http://dx.doi.org/10.1038/nature03063.

Mizumoto, K., Yamamoto, T., Nishiura, H., 2013. Age-dependent estimates of the epidemiological impact of pandemic influenza (H1N1-2009) in Japan. Comput. Math. Methods Med. 2013, 1–8. http://dx.doi.org/10.1155/2013/637064.

Monto, A.S., 2004. Global burden of influenza: what we know and what we need to know. Int. Congr. Ser. 1263, 3–11. http://dx.doi.org/10.1016/j.ics.2004.02.049.

Mozdzanowska, K., Maiese, K., Furchner, M., Gerhard, W., 1999. Treatment of influenza virus-infected SCID mice with nonneutralizing antibodies specific for the transmembrane proteins matrix 2 and neuraminidase reduces the pulmonary virus titer but fails to clear the infection. Virology 254 (1), 138–146. http://dx.doi.org/10.1006/viro.1998.9534.

Murphy, B.R., Kasel, J.A., Chanock, R.M., 1972. Association of serum anti-neuraminidase antibody with resistance to influenza in man. N. Engl. J. Med. 286 (25), 1329–1332. http://dx.doi.org/10.1056/nejm197206222862502.

National Institute of Infectious Diseases, 2020. Isolation/detection of influenza virus in Japan, 2017/18 season. https://www.niid.go.jp/niid/en/influenza-e.html. (Accessed 30 November 2020).

Neumann, G., Kawaoka, Y., 2019. Predicting the next influenza pandemics. J. Infect. Dis. 219 (Suppl. 1), S14–S20. http://dx.doi.org/10.1093/infdis/jiz040.

Nguyen, H.H., Zemlin, M., Ivanov, I.I., Andrasi, J., Zemlin, C., Vu, H.L., et al., 2007. Heterosubtypic immunity to influenza a virus infection requires a properly diversified antibody repertoire. J. Virol. 81 (17), 9331–9338. http://dx.doi.org/10.1128/jvi.00751-07.

Nishiura, H., 2011. Real-time forecasting of an epidemic using a discrete time stochastic model: a case study of pandemic influenza (H1N1-2009). Biomed. Eng. Online 10 (1), 15. http://dx.doi.org/10.1186/1475-925x-10-15.

Ohkusa, Y., Sugawara, T., Taniguchi, K., Okabe, N., 2011. Real-time estimation and prediction for pandemic A/H1N1 (2009) in Japan. J. Infect. Chemother. 17 (4), 468–472. http://dx.doi.org/10.1007/s10156-010-0200-3.

Ohkusa, Y., Sugawara, T., et al., 2009. Simulation model of pandemic influenza in the whole of Japan. Jpn. J. Infect. Dis. 62 (2), 98–106.

Omori, R., Nishiura, H., 2011. Theoretical basis to measure the impact of short-lasting control of an infectious disease on the epidemic peak. Theor. Biol. Med. Model. 8 (1), http://dx.doi.org/10.1186/1742-4682-8-2.

Padilla-Quirarte, H.O., Lopez-Guerrero, D.V., Gutierrez-Xicotencatl, L., Esquivel-Guadarrama, F., 2019. Protective antibodies against influenza proteins. Front. Immunol. 10, http://dx.doi.org/10.3389/fimmu.2019.01677.

Penman, B.S., Gupta, S., Shanks, G.D., 2016. Rapid mortality transition of Pacific Islands in the 19th century. Epidemiol. Infect. 145 (1), 1–11. http://dx.doi.org/10.1017/s0950268816001989.

Petrova, V.N., Russell, C.A., 2017. The evolution of seasonal influenza viruses. Nat. Rev. Microbiol. 16 (1), 47–60. http://dx.doi.org/10.1038/nrmicro.2017.118.

Pouillot, R., Lachenal, G., Pybus, O.G., Rousset, D., Njouom, R., 2008. Variable epidemic histories of hepatitis C virus genotype 2 infection in West Africa and Cameroon. Infect. Genet. Evol. 8 (5), 676–681. http://dx.doi.org/10.1016/j.meegid.2008.06.001.

Pourbohloul, B., Ahued, A., Davoudi, B., Meza, R., Meyers, L.A., Skowronski, D.M., et al., 2009. Initial human transmission dynamics of the pandemic (H1N1) 2009 virus in North America. Influenza Other Respir. Viruses 3 (5), 215–222. http://dx.doi.org/10.1111/j.1750-2659.2009.00100.x.

Rajaram, S., Wiecek, W., Lawson, R., Blak, B.T., Zhao, Y., Hackett, J., et al., 2017. Impact of increased influenza vaccination in 2–3-year-old children on disease burden within the general population: A Bayesian model-based approach. PLoS One 12 (12), e0186739. http://dx.doi.org/10.1371/journal.pone.0186739.

Reichert, T., Chowell, G., McCullers, J.A., 2012. The age distribution of mortality due to influenza: pandemic and peri-pandemic. BMC Med. 10 (1), 162. http://dx.doi.org/10.1186/1741-7015-10-162.

Reluga, T.C., Medlock, J., Perelson, A.S., 2008. Backward bifurcations and multiple equilibria in epidemic models with structured immunity. J. Theoret. Biol. 252 (1), 155–165. http://dx.doi.org/10.1016/j.jtbi.2008.01.014.

Schulman, J.L., Khakpour, M., Kilbourne, E.D., 1968. Protective effects of specific immunity to viral neuraminidase on influenza virus infection of mice. J. Virol. 2 (8), 778–786. http://dx.doi.org/10.1128/jvi.2.8.778-786.1968.

Skountzou, I., Koutsonanos, D.G., Kim, J.H., Powers, R., Satyabhama, L., Masseoud, F., et al., 2010. Immunity to pre-1950 H1N1 influenza viruses confers cross-protection against the pandemic swine-origin 2009 A (H1N1) influenza virus. J. Immunol. 185 (3), 1642–1649. http://dx.doi.org/10.4049/jimmunol.1000091.

Spiegelhalter, D.J., Best, N.G., Carlin, B.P., van der Linde, A., 2002. Bayesian measures of model complexity and fit. J. R. Stat. Soc. Ser. B Stat. Methodol. 64 (4), 583–639. http://dx.doi.org/10.1111/1467-9868.00353.

Sym, D., Patel, P.N., Ei-Chaar, G.M., 2009. Seasonal, avian, and novel H1N1 influenza: Prevention and treatment modalities. Ann. Pharmacother. 43 (12), 2001–2011. http://dx.doi.org/10.1345/aph.1m557.

Taubenberger, J.K., Morens, D.M., 2006. 1918 influenza: the mother of all pandemics. Emerg. Infect. Diseases 12 (1), 15–22. http://dx.doi.org/10.3201/eid1209.05-0979.

Thompson, R.N., 2020b. Epidemiological models are important tools for guiding COVID-19 interventions. BMC Med. 18 (1), http://dx.doi.org/10.1186/s12916-020-01628-4.

Thompson, R.N., 2020c. Novel coronavirus outbreak in Wuhan, China, 2020: Intense surveillance is vital for preventing sustained transmission in new locations. J. Clin. Med. 9 (2), 498. http://dx.doi.org/10.3390/jcm9020498.

Thompson, R.N., Brooks-Pollock, E., 2019. Detection, forecasting and control of infectious disease epidemics: modelling outbreaks in humans, animals and plants. Philos. Trans. R. Soc. B 374 (1775), 20190038. http://dx.doi.org/10.1098/rstb.2019.0038.

Thompson, R.N., Gilligan, C.A., Cunniffe, N.J., 2016. Detecting presymptomatic infection is necessary to forecast major epidemics in the earliest stages of infectious disease outbreaks. PLoS Comput. Biol. 12 (4), e1004836. http://dx.doi.org/10.1371/journal.pcbi.1004836.

Thompson, R.N., Gilligan, C.A., Cunniffe, N.J., 2020a. Will an outbreak exceed available resources for control? Estimating the risk from invading pathogens using practical definitions of a severe epidemic. J. R. Soc. Interface 17 (172), 20200690. http://dx.doi.org/10.1098/rsif.2020.0690.

Thompson, R.N., Hart, W.S., 2018. Effect of confusing symptoms and infectiousness on forecasting and control of Ebola outbreaks. Clin. Inf. Dis. 67 (9), 1472–1474. http://dx.doi.org/10.1093/cid/ciy248.

Thompson, R.N., Hollingsworth, T.D., Isham, V., Arribas-Bel, D., Ashby, B., Britton, T., et al., 2020d. Key questions for modelling COVID-19 exit strategies. Proc. R. Soc. B 287 (1932), 20201405. http://dx.doi.org/10.1098/rspb.2020.1405.

Thompson, R.N., Thompson, C.P., Pelerman, O., Gupta, S., Obolski, U., 2019. Increased frequency of travel in the presence of cross-immunity may act to decrease the chance of a global pandemic. Philos. Trans. R. Soc. B 374 (1775), 20180274. http://dx.doi.org/10.1098/rstb.2018.0274.

Tizzoni, M., Bajardi, P., Poletto, C., Ramasco, J.J., Balcan, D., Gonçalves, B., et al., 2012. Real-time numerical forecast of global epidemic spreading: case study of 2009 A/H1N1pdm. BMC Med. 10 (1), http://dx.doi.org/10.1186/1741-7015-10-165.

Trifonov, V., Khiabanian, H., Rabadan, R., 2009. Geographic dependence, surveillance, and origins of the 2009 influenza A (H1N1) virus. N. Engl. J. Med. 361 (2), 115–119. http://dx.doi.org/10.1056/nejmp0904572.

Tuite, A.R., Greer, A.L., Whelan, M., Winter, A.-L., Lee, B., Yan, P., et al., 2009. Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza. Can. Med. Assoc. J. 182 (2), 131–136. http://dx.doi.org/10.1503/cmaj.091807.

Volz, E., Meyers, L.A., 2007. Susceptible–infected–recovered epidemics in dynamic contact networks. Proc. R. Soc. B 274 (1628), 2925–2934. http://dx.doi.org/10.1098/rspb.2007.1159.

Volz, E.M., Miller, J.C., Galvani, A., Meyers, L.A., 2011. Effects of heterogeneous and clustered contact patterns on infectious disease dynamics. PLoS Comput. Biol. 7 (6), e1002042. http://dx.doi.org/10.1371/journal.pcbi.1002042.

Webster, R., Reay, P., Laver, W., 1988. Protection against lethal influenza with neuraminidase. Virology 164 (1), 230–237. http://dx.doi.org/10.1016/0042-6822(88)90640-x.

Weiss, H.H., 2013. The SIR model and the foundations of public health. Mater. Mat. (3), 1–17, https://ddd.uab.cat/record/108432.

Xing, Z., Cardona, C.J., 2009. Preexisting immunity to pandemic (H1N1) 2009. Emerg. Infect. Diseases 15 (11), 1847–1849. http://dx.doi.org/10.3201/eid1511.090685.

Xu, R., Ekiert, D.C., Krause, J.C., Hai, R., Crowe, J.E., Wilson, I.A., 2010. Structural basis of preexisting immunity to the 2009 H1N1 pandemic influenza virus. Science 328 (5976), 357–360. http://dx.doi.org/10.1126/science.1186430.

Yang, W., Lipsitch, M., Shaman, J., 2015. Inference of seasonal and pandemic influenza transmission dynamics. Proc. Natl. Acad. Sci. USA 112 (9), 2723–2728. http://dx.doi.org/10.1073/pnas.1415012112.

Yu, X., Tsibane, T., McGraw, P.A., House, F.S., Keefer, C.J., Hicar, M.D., et al., 2008. Neutralizing antibodies derived from the B cells of 1918 influenza pandemic survivors. Nature 455 (7212), 532–536. http://dx.doi.org/10.1038/nature07231.