The influenza pandemic preparedness planning tool *InfluSim*

M Eichner[1], M Schwehm[1§], HP Duerr[1], SO Brockmann[2]

[1] Department of Medical Biometry, University of Tübingen, Germany
[2] Baden-Württemberg State Health Office, District Government Stuttgart, Germany

Description of the transmission dynamics of InfluSim version 2.0

Susceptible individuals $S_{a,r}$ are infected at a rate $\lambda_a(t)$ which depends on their age a and on time t. Infected individuals, $E_{a,r}$, incubate the infection for a mean duration D_E. To obtain a realistic distribution of this duration, the incubation period is modelled in n stages so that progression from one stage to the next one occurs at rate $\delta = n / D_E$. The last l incubation stages are regarded as early infectious period during which patients may already spread the infection (this accounts for an average time of $l\, D_E / n$ for the "early infectious period" which is about half a day for the standard set of parameters). After passing through the last incubation stage, infected individuals become fully contagious and a fraction of them develops clinical symptoms. The course of disease depends on the age a of the infected individual and on the risk category r to which he or she belongs: a fraction $c_{a,r}(A)$ becomes asymptomatic (A_a), a fraction $c_{a,r}(M)$ becomes moderately sick (M_a), a fraction $c_{a,r}(V)$ becomes very sick (V_a) and the remaining fraction $c_{a,r}(X)$ becomes extremely sick (X_a) and need hospitalization (i.e., $c_{a,r}(A)$ + $c_{a,r}(M)$ + $c_{a,r}(V)$ + $c_{a,r}(X)$ = 1 for each combination of a and r). The rationale for distinguishing very sick and extremely sick cases is that only extremely sick cases can die from the disease and need to be hospitalized; in all other aspects, both groups of severe cases are assumed to be identical. The duration of the fully contagious stage depends on the course of the disease and on the age of the case. Sojourn times are $D_{A,a}$ and $D_{M,a}$ for asymptomatic and moderately sick cases, respectively, and $D_{V,a}$ for both groups of severe cases. To obtain realistic distributions of these sojourn times, the contagious classes are modelled in m stages each so that progression from one stage to the next occurs at rate $\gamma_{A,a} = m / D_{A,a}$, $\gamma_{M,a} = m / D_{M,a}$ and $\gamma_{V,a,U} = m / D_{V,a}$, respectively. Severe cases seek medical help on average D_D days after onset. Assuming that the waiting time until visiting a doctor is exponentially distributed, we use a constant rate $\alpha = 1 / D_D$ for doctoral visits. Very sick patients (V_a) who visit a doctor are advised to withdraw to their home (W_a) until the disease is over whereas extremely sick cases (X_a) are immediately hospitalized (H_a). A fraction $f_V(t)$ of all severe and a fraction

$f_X(t)$ of all extremely severe cases who visit the doctor within D_T days after onset of symptoms are offered antiviral treatment, given that its supply has not yet been exhausted. As our model does not explicitly consider the age of the disease (which would demand partial differential equations), we use the contagious stages to measure time since onset and allow for treatment up to stage $m_{a,T}$ (see below for details). This imposes some variability to the maximum time until which treatment can be given, which may even improve the realism of the model with respect to real-life scenarios. Antiviral treatment reduces the patients' contagiousness by f_I percent and it reduces hospitalization and death by f_H percent. Extremely sick patients, whose hospitalization is prevented by treatment, are sent home and join the group of treated very sick patients $(W_{a,T})$. The remaining duration of disease and contagiousness of treated cases is reduced by f_D percent so that their rate of progressing from one stage to the next has to be changed to $\gamma_{V,a,T} = m/((1-f_D)D_{V,a})$. Extremely sick and hospitalized cases die at rates τ_a, depending on their age a. Whereas asymptomatic (A_a) and moderately sick patients (M_a) who have passed their last stage of contagiousness are considered healthy immunes (I), very sick and extremely sick patients (classes V_a, $W_{a,U}$, $W_{a,T}$, X_a, $H_{a,U}$ and $H_{a,T}$) first become convalescent (C_a) for an average duration of D_C days before they resume their ordinary life. To obtain a realistic distribution of this sojourn time, convalescence is modelled in j stages so that progression from one stage to the next occurs at rate $\rho = j/D_C$. Fully recovered patients who have passed through their last stage of convalescence join the group of healthy immunes I; working adults will go back to work. Further interventions, describing the reduction of contacts, will be discussed after the presentation of the differential equations.

Differential equation model describing the transmission dynamics

Susceptible individuals

$$\dot{S}_{a,r} = -\lambda_a(t)S_{a,r}$$

Infected individuals who incubate the infection

$$\dot{E}_{1,a,r} = \lambda_a(t)\,S_{a,r} - \delta E_{1,a,r}$$

$$\dot{E}_{k,a,r} = \delta(E_{k-1,a,r} - E_{k,a,r}) \qquad \text{for } k = 2,\ldots,n$$

Asymptomatic infectious individuals

$$\dot{A}_{1,a} = \delta\, c_{a,r}(A)\,E_{n,a,r} - \gamma_{A,a}A_{1,a}$$

$$\dot{A}_{k,a} = \gamma_{A,a}(A_{k-1,a} - A_{k,a}) \qquad \text{for } k = 2,\ldots,m$$

Moderately sick individuals

$$\dot{M}_{1,a} = \delta\, c_{a,r}(M)\,E_{n,a,r} - \gamma_{M,a}M_{1,a}$$

$$\dot{M}_{k,a} = \gamma_{M,a}(M_{k-1,a} - M_{k,a}) \qquad \text{for } k = 2,\ldots,m$$

Very sick individuals who have not yet visited a doctor

$$\dot{V}_{1,a} = \delta c_{a,r}(V)\, E_{n,a,r} - (\gamma_{V,a,U} + \alpha) V_{1,a}$$

$$\dot{V}_{k,a} = \gamma_{V,a,U}(V_{k-1,a} - V_{k,a}) - \alpha V_{k,a} \qquad \text{for } k = 2,\ldots,m$$

Treated very sick individuals

$$\dot{W}_{1,a,T} = \alpha(f_V(t) V_{1.a} + f_X(t)\, f_H X_{1,a}) - \gamma_{V,a,T} W_{1,a,T}$$

$$\dot{W}_{k,a,T} = \alpha(f_V(t) V_{k,a} + f_X(t)\, f_H X_{k,a}) + \gamma_{V,a,T}(W_{k-1,a,T} - W_{k,a,T}) \quad \text{for } k = 2,\ldots,m_{a,T}$$

$$\dot{W}_{k,a,T} = \gamma_{V,a,T}(W_{k-1,a,T} - W_{k,a,T}) \qquad \text{for } k = m_{a,T} + 1,\ldots,m$$

Untreated very sick individuals

$$\dot{W}_{1,a,U} = \alpha(1 - f_V(t)) V_{1,a} - \gamma_{V,a,U} W_{1,a,U}$$

$$\dot{W}_{k,a,U} = \alpha(1 - f_V(t)) V_{k,a} + \gamma_{V,a,U}(W_{k-1,a,U} - W_{k,a,U}) \qquad \text{for } k = 2,\ldots,m_{a,T}$$

$$\dot{W}_{k,a,U} = \alpha V_{k,a} + \gamma_{V,a,U}(W_{k-1,a,U} - W_{k,a,U}) \qquad \text{for } k = m_{a,T} + 1,\ldots,m$$

Extremely sick individuals who have not yet visited a doctor

$$\dot{X}_{1,a} = \delta c_{a,r}(X)\, E_{n,a,r} - (\gamma_{V,a} + \alpha + \tau_a) X_{1,a}$$

$$\dot{X}_{k,a} = \gamma_{V,a}(X_{k-1,a} - X_{k,a}) - (\alpha + \tau_a) X_{k,a} \qquad \text{for } k = 2,\ldots,m$$

Hospitalized and treated cases

$$\dot{H}_{1,a,T} = \alpha f_X(t)(1 - f_H) X_{1,a} - (\gamma_{V,a,T} + \tau_a) H_{1,a,T}$$

$$\dot{H}_{k,a,T} = \alpha f_X(t)(1 - f_H) X_{k,a} + \gamma_{V,a,T}(H_{k-1,a,T} - H_{k,a,T}) - \tau_a H_{k,a,T} \qquad \text{for } k = 2,\ldots,m_{a,T}$$

$$\dot{H}_{k,a,T} = \gamma_{V,a,T}(H_{k-1,a,T} - H_{k,a,T}) - \tau_a H_{k,a,T} \qquad \text{for } k = m_{a,T} + 1,\ldots,m$$

Hospitalized, but untreated cases

$$\dot{H}_{1,a,U} = \alpha(1 - f_X(t)) X_{1,a} - (\gamma_{V,a,U} + \tau_a) H_{1,a,U}$$

$$\dot{H}_{k,a,U} = \alpha(1 - f_X(t)) X_{k,a} + \gamma_{V,a,U}(H_{k-1,a,U} - H_{k,a,U}) - \tau_a H_{k,a,U} \qquad \text{for } k = 2,\ldots,m_{a,T}$$

$$\dot{H}_{k,a,U} = \alpha X_{k,a} + \gamma_{V,a,U}(H_{k-1,a,U} - H_{k,a,U}) - \tau_a H_{k,a,U} \qquad \text{for } k = m_{a,T} + 1,\ldots,m$$

Contact rates and basic reproduction number

Contact matrix

For the mixing of the age classes, we employ a who-acquires-infection-from whom matrix $\mathbf{M} = (\mathbf{m}_{a_s,a_i})$ which gives the relative frequency of contacts of infective individuals of age a_i with other people of age a_s. In this paper, we assume bi-directional contacts (e.g. children have the same total number of contacts with adults as adults with children). Multiplication of this matrix with an appropriate constant scaling factor κ (see below) results in the matrix of crude contact rates $\beta_{a_s,a_i} = \kappa \mathbf{m}_{a_s,a_i}$.

Contagiousness of the different types of disease

In the absence of interventions, we have to multiply these contact rates with the contagiousness factors b_L, b_A, b_M and b_V to obtain the effective contact rates:

$\beta_{L,a_s,a_i} = b_L \beta_{a_s,a_i}$ during the early infectious period,

$\beta_{A,a_s,a_i} = b_A \beta_{a_s,a_i}$ of asymptomatic cases,

$\beta_{M,a_s,a_i} = b_M \beta_{a_s,a_i}$ of moderately sick cases,

$\beta_{V,a_s,a_i} = b_V \beta_{a_s,a_i}$ of (untreated) very sick cases.

Day care centres and schools

To assess the effect of day care centre and school closing on the transmission of an infectious disease, we have to first make an assumption on what fraction r_{sch} of the contacts among healthy children who are in the same age class occurs in day care centres and schools. The contact rates between very sick or hospitalized children (who do not attend day care centre or school) and other children need, therefore, be reduced to $\beta'_{V,a_s,a_i}(t) = (1 - r_{sch})\beta_{V,a_s,a_i}$ (contact rate between healthy and very sick children in the same age class, i.e. $a_i = a_s$).

As very sick children have to be taken care of by adults at home or in hospital, their contact rate to adults increases by a factor :

$\beta'_{V,a_s,a_i}(t) = \beta_{V,a_s,a_i} F_{HC}$ (contact rate between very sick children of age a_i and adults of age a_s).

Contacts between very sick children and other children in a higher or lower age class remain unchanged:

$\beta'_{V,a_s,a_i}(t) = \beta_{V,a_s,a_i}$ (contact rate between healthy children of age a_s and very sick children of a different age a_i).

Closing of day care centres and schools

Closing day care centres and schools at time t will not necessarily prevent all the contacts that would have happened with other children. During the closing of schools and day care centres, the contact rates between susceptible children of age a_s and infected children of age a_i who are in their late incubation period (β_{L,a_s,a_i}), who are asymptomatic (β_{A,a_s,a_i}), or who are moderately sick (β_{M,a_s,a_i}) are reduced by the factor r_{sch} if the children are in the same age class:

$$\beta'_{L,a_s,a_i}(t) = \begin{cases} \beta_{L,a_s,a_i}(1 - r_{sch})^{\mathbf{1}_{sch}(t)} & if \quad a_s = a_i \\ \beta_{L,a_s,a_i} & if \quad a_s \neq a_i, \end{cases}$$

$$\beta'_{A,a_s,a_i}(t) = \begin{cases} \beta_{A,a_s,a_i}(1 - r_{sch})^{\mathbf{1}_{sch}(t)} & if \quad a_s = a_i \\ \beta_{A,a_s,a_i} & if \quad a_s \neq a_i, \end{cases}$$

$$\beta'_{M,a_s,a_i}(t) = \begin{cases} \beta_{M,a_s,a_i}(1 - r_{sch})^{\mathbf{1}_{sch}(t)} & if \quad a_s = a_i \\ \beta_{M,a_s,a_i} & if \quad a_s \neq a_i. \end{cases}$$

where $\mathbf{1}_{sch}(t)$ is a function which indicates when schools and day care centres are opened or closed:

$$\mathbf{1}_{sch}(t)=\begin{cases}1 & \text{while day care centres and schools are closed}\\ 0 & \text{while day care centres and schools are opened.}\end{cases}$$

While day care centres and schools are closed, children (age a_i) need adult supervision at home. Their contact with susceptible adults (age a_s) increases by the "child care factor" F_{CC}:

$$\beta'_{L,a_s,a_i}(t)=\beta_{L,a_s,a_i}\left(F_{CC}\right)^{\mathbf{1}_{sch}(t)},$$
$$\beta'_{A,a_s,a_i}(t)=\beta_{A,a_s,a_i}\left(F_{CC}\right)^{\mathbf{1}_{sch}(t)},$$
$$\beta'_{M,a_s,a_i}(t)=\beta_{M,a_s,a_i}\left(F_{CC}\right)^{\mathbf{1}_{sch}(t)},$$

Child care at home also increases the exposure of healthy children (age a_s) to contagious adults (age a_i):

$$\beta'_{L,a_s,a_i}(t)=\beta_{L,a_s,a_i}\left(F_{CC}\right)^{\mathbf{1}_{sch}(t)},$$
$$\beta'_{A,a_s,a_i}(t)=\beta_{A,a_s,a_i}\left(F_{CC}\right)^{\mathbf{1}_{sch}(t)},$$
$$\beta'_{M,a_s,a_i}(t)=\beta_{M,a_s,a_i}\left(F_{CC}\right)^{\mathbf{1}_{sch}(t)},$$
$$\beta'_{V,a_s,a_i}(t)=\beta_{V,a_s,a_i}\left(F_{CC}\right)^{\mathbf{1}_{sch}(t)}.$$

Cancelling of mass gathering events

Cancelling mass gathering events effects only the contacts of adults who are healthy enough to attend such events. Assuming that such an intervention at time t reduces contacts by a fraction r_{mass}, we get for all contacts between susceptible adults of age a_s and infectious adults of age a_i the following contact rates:

$$\beta'_{L,a_s,a_i}(t)=\beta_{L,a_s,a_i}(1-r_{mass})^{\mathbf{1}_{mass}(t)},$$
$$\beta'_{A,a_s,a_i}(t)=\beta_{A,a_s,a_i}(1-r_{mass})^{\mathbf{1}_{mass}(t)},$$
$$\beta'_{M,a_s,a_i}(t)=\beta_{M,a_s,a_i}(1-r_{mass})^{\mathbf{1}_{mass}(t)}.$$

where $\mathbf{1}_{mass}(t)$ is a function which indicates when mass gathering events are possible or when they are closed:

$$\mathbf{1}_{mass}(t)=\begin{cases}1 & \text{while mass gathering events are forbidden}\\ 0 & \text{while mass gathering events are allowed.}\end{cases}$$

As contacts with adults who are too sick to attend such mass gathering events cannot be prevented by this measure it is

$$\beta'_{V,a_s,a_i}(t)=\beta_{V,a_s,a_i}.$$

General reduction of contacts

During some time in the epidemic, the general population may effectively reduce contacts which can be a result of wearing facial masks, increasing “social distance”, adopting improved measures of “respiratory hygiene” or simply of a general change in behaviour. This will be implemented in the program by reducing the contacts of susceptible individuals at that time t by factor $r_{gen}(t)$. The adjusted contact rates are:

$$\beta''_{L,a_s,a_i}(t)=\beta'_{L,a_s,a_i}(t)\left(1-r_{gen}\right)^{\mathbf{1}_{gen}(t)} \qquad \text{for cases in the late incubation period,}$$
$$\beta''_{A,a_s,a_i}(t)=\beta'_{A.a_s,a_i}(t)\left(1-r_{gen}\right)^{\mathbf{1}_{gen}(t)} \qquad \text{for asymptomatic cases,}$$

$\beta''_{M,a_s,a_i}(t) = \beta'_{M.a_s,a_i}(t)\left(1-r_{gen}\right)^{\mathbf{1}_{gen}(t)})$ for moderately sick cases,

$\beta''_{V,a_s,a_i}(t) = \beta'_{V,a_s,a_i}(t)\left(1-r_{gen}\right)^{\mathbf{1}_{gen}(t)}$ for very sick cases,

where $\mathbf{1}_{gen}(t)$ is a function which indicates when the population reduces their contacts:

$$\mathbf{1}_{gen}(t) = \begin{cases} 1 & \text{while the population reduces their contacts} \\ 0 & \text{while the population behaves as usual.} \end{cases}$$

Partial isolation of cases

If cases are (partly) isolated, their contact rates are reduced by factors $\left(1-r_{iso_M}\right)$, $\left(1-r_{iso_V}\right)$ and $\left(1-r_{iso_H}\right)$, respectively, resulting in contact rates

$\beta'''_{M,a_s,a_i}(t) = \beta''_{M,a_s,a_i}(t)\left(1-r_{iso_M}\right)^{\mathbf{1}_{iso}(t)}$ for moderately sick cases,

$\beta'''_{V,a_s,a_i}(t) = \beta''_{V,a_s,a_i}(t)\left(1-r_{iso_V}\right)^{\mathbf{1}_{iso}(t)}$ for very sick cases at home,

$\beta'''_{H,a_s,a_i}(t) = \beta''_{V,a_s,a_i}(t)\left(1-r_{iso_H}\right)^{\mathbf{1}_{iso}(t)}$ for hospitalized very sick cases,

where $\mathbf{1}_{iso}(t)$ is a function which indicates when mass gathering events are possible or when they are closed:

$$\mathbf{1}_{iso}(t) = \begin{cases} 1 & \text{while isolation measures are performed} \\ 0 & \text{while no isolation measures are performed.} \end{cases}$$

The contact rates of cases in the late incubation period and that of asymptomatic cases remain unchanged:

$\beta'''_{L,a_s,a_i}(t) = \beta''_{L,a_s,a_i}(t)$ for infected individuals in the late incubation period,

$\beta'''_{A,a_s,a_i}(t) = \beta''_{A,a_s,a_i}(t)$ for asymptomatic cases.

Course of contagiousness

To allow for a contagiousness which changes over the course of disease, we multiply each contact rate with a weighting factor $p_k = x^{k-1} \Big/ \sum_{i=0}^{m-1} x^i$ whereby k is the stage of contagiousness. This leads to the following contact rates:

$\beta_{A_k,a_s,a_i}(t) = \beta'''_{A,a_s,a_i}(t)\ p_k$ for asymptomatic cases in stage k,

$\beta_{M_k,a_s,a_i}(t) = \beta'''_{M,a_s,a_i}(t)\, p_k$ for moderately sick cases in stage k,

$\beta_{V_k,a_s,a_i}(t) = \beta'''_{V,a_s,a_i}(t)\, p_k$ for very sick cases in stage k,

$\beta_{H_k,a_s,a_i}(t) = \beta'''_{H,a_s,a_i}(t)\, p_k$ for hospitalized cases in stage k.

For $x = 1$, contagiousness is equally high in all stages; for $x = 0$, only the first stage is contagious; for $0 < x < 1$, the contagiousness decreases in a geometric procession. We make the simplifying assumption that contagiousness does not change during the late incubation period

$\beta_{L_k,a_s,a_i}(t) = \beta'''_{L,a_s,a_i}(t)$ for cases in stage $k = n-l,..,n$ of the incubation period.

Next generation matrix and basic reproduction number

At time $t = 0$ and in the absence of interventions, the next generation matrix has the following elements

$$n_{a_s,a_i} = \left(\frac{1}{n} \sum_{k=n-l+1}^{n} \beta_{L_k,a_s,a_i}(0) D_E + \frac{1}{m} \sum_r \sum_{k=1}^{m} \left(\begin{array}{l} c_{a_i,r}(A)\,\beta_{A_k,a_s,a_i}(0)\,D_{A,a_i} \\ + c_{a_i,r}(M)\,\beta_{M_k,a_s,a_i}(0)\,D_{M,a_i} \\ + \left(c_{a_i,r}(V) + c_{a_i,r}(X)(1-d_{a_i}) \right) \beta_{V_k,a_s,a_i}(0)\,D_{V,a_i} \end{array} \right) \right)$$

where d_{a_i} is the fraction of untreated extremely severe cases who die from the disease (see below for details). The dominant eigenvalue of this matrix is called the basic reproduction number R_0. If κ (which determines the value of the contact rates $\beta_{\bullet_k,a_s,a_i}$) is given, the eigenvectors of this matrix can numerically be calculated. The user-specified value of R_0 is now used to determine numerically the scaling factor κ. Let $\vec{\mathbf{e}} = (\mathbf{e}_{a_i})$ be the eigenvector which has the largest eigenvalue R_0.

Force of infection

To calculate the force of infection $\lambda_{a_s}(t)$ to which susceptible individuals of age a_s are exposed at time t, we have to first calculate the product of the number of contagious individuals with the corresponding contact rates and then to sum up these products over all ages a_i, all risk categories r, all courses of the disease and all stages. Assuming that the contagiousness of cases who have received antiviral treatment is reduced by the factor $(1 - f_C)$, the force of infection is given by

$$\lambda_{a_s}(t) = \sum_{a_i} \left(\sum_r \sum_{k=n-l+1}^{n} \beta_{L_k,a_s,a_i}(t) E_{k,a_i,r} + \sum_{k=1}^{m} \left(\begin{array}{l} \beta_{A_k,a_s,a_i}(t)\,A_{k,a_i} + \beta_{M_k,a_s,a_i}(t)\,M_{k,a_i} \\ + \beta_{V_k,a_s,a_i}(t) \left(V_{k,a_i} + W_{k,a_i,U} + (1-f_I) W_{k,a_i,T} + X_{k,a_i} \right) \\ + \beta_{H_k,a_s,a_i}(t) \left(H_{k,a_i,U} + (1-f_I) H_{k,a_i,T} \right) \end{array} \right) \right)$$

Differential equations for various model output

Cumulative number of deaths

$$\dot{D} = \sum_a \sum_{k=1}^{m} \left(\tau_{a,U} \left(X_a + H_{k,a,U} \right) + \tau_a H_{k,a,T} \right)$$

Convalescent (but non-contagious) cases

$$\dot{C}_{1,a} = \gamma_{V,a,U} \left(V_{m,a} + W_{m,a,U} + X_{m,a} + H_{m,a,U} \right) + \gamma_{V,a,T} \left(V_{m,a,T} + H_{m,a,T} \right) - \rho C_{1,a}$$

$$\dot{C}_{k,a} = \rho (C_{k-1,a} + C_{k,a}) \qquad \text{for } k = 2,\ldots,j$$

Immune and fully recovered individuals

$$\dot{I} = \sum_a \left(\rho C_{j,a} + \gamma_A A_{m,a} + \gamma_M M_{m,a} \right)$$

Number of people who are unable to work because of influenza

$$\dot{U} = \sum_{a_W} \left(\sum_r \delta E_{n,a_W,r} (c_{a_W,r}(V) + c_{a_W,r}(X)) - \tau_{a_W} \sum_{k=1}^{m} \left(X_{k,a_W} + H_{k,a_W,U} + H_{k,a_W,T} \right) - \rho C_{j,a_W} \right)$$

where a_W denote all age classes of working adults (to avoid infinite contributions to the work loss, the decision was made that cases who die from influenza do not contribute any further to the total work loss).

Cumulative doses of antiviral treatment

$$\dot{T} = \alpha \sum_{k=1}^{m_{a,T}} \sum_{a} (f_V(t) V_{k,a} + f_X(t) X_{k,a})$$

Initial values

Using the user-specified numbers of people N_a in the age classes and the fractions F_a of people under high risk within each age class (Table 2), we obtain the initial population sizes according to age and risk class: $N_{a,r_1}(0) = N_a(1 - F_a)$ and $N_{a,r_2}(0) = N_a F_a$. The total population is, therefore, given by $N(0) = \sum_a \sum_r N_{a,r}(0)$. At time $t = 0$, one infection is introduced into an otherwise fully susceptible population. To avoid biasing the simulation one way or the other, the initial infection is distributed over all classes, weighted by the probability that an individual in one class acquires the infection (i.e. by the component of the eigenvector $\vec{\mathbf{e}} = (\mathbf{e}_a)$ of the next generation matrix):

$$S_{a,r}(0) = N_{a,r}(0) - \begin{cases} (1 - F_r)\mathrm{e}_a \Big/ \sum_{a_i} \mathrm{e}_{a_i} & \text{if } r = r_1 \quad \text{(low risk group)} \\ F_r\, \mathrm{e}_a \Big/ \sum_{a_i} \mathrm{e}_{a_i} & \text{if } r = r_2 \quad \text{(high risk group)} \end{cases}$$

$$E_{k,a,r}(0) = \begin{cases} (1 - F_r) F_r\, \mathrm{e}_a \Big/ \sum_{a_i} \mathrm{e}_{a_i} & \text{if } r = r_1 \quad \text{(low risk group) and } k = 1 \\ F_r\, \mathrm{e}_a \Big/ \sum_{a_i} \mathrm{e}_{a_i} & \text{if } r = r_2 \quad \text{(high risk group) and } k = 1 \\ 0 & \text{if } k > 1 \end{cases}$$

$\forall_{k=1}^{m}\ A_{k,a}(0) = M_{k,a}(0) = V_{k,a}(0) = W_{k,a,U}(0) = W_{k,a,T}(0) = X_{k,a}(0) = H_{k,a,U}(0) = H_{k,a,T}(0) = 0$

$\forall_{k=1}^{j}\ C_{k,a}(0) = 0$, $D(0) = I(0) = U(0) = T(0) = 0$.

Using these initial values, the set of differential equations is solved numerically with a Runge-Kutta method with step-size control.

Abbreviations

Model variables

Transmission variables

$S_{a,r}$	number of susceptible individuals
$E_{k,a,r}$	number of incubating individuals (stage k); the last two stages are contagious
$A_{k,a}$	number of asymptomatic individuals (stage k)
$M_{k,a}$	number of moderately sick individuals (stage k)
$V_{k,a}$	number of very sick individuals who have not yet seen a doctor (stage k)
$W_{k,a,T}$	number of treated very sick individuals (withdrawn to home; stage k)
$W_{k,a,U}$	number of untreated very sick individuals (withdrawn to home; stage k)
$X_{k,a}$	number of extremely sick individuals who have not seen a doctor (stage k)
$H_{k,a,T}$	number of hospitalized and treated individuals (stage k)
$H_{k,a,U}$	number of hospitalized but untreated individuals (stage k)

Output variables

$C_{k,a}$	number of convalescent (non-contagious) cases (stage k)
I	number of fully recovered and immune cases
D	number of people who die of influenza
U	number of people who are unable to work because of influenza
T	cumulative number of antiviral treatment doses used

Parameters concerning the demography

N_a	total population size by age class a, whereby $a = a_1$ denotes children, $a = a_2$ denotes adults of working age and $a = a_2$ denotes elderly, respectively.
F_a	fraction of the population in age class a which is under high risk from this, $N_{a,r}$ is calculated such that $N_{a,r} = F_a r_a$
K_{a_s,a_i}	the contact matrix gives the weekly number of contacts between an individual of age class a_i with individuals of age class a_s. From this, the contact rates $\beta_{L_k,a_s,a_i}(t)$, $\beta_{A_k,a_s,a_i}(t)$, $\beta_{M_k,a_s,a_i}(t)$ and $\beta_{V_k,a_s,a_i}(t)$ are calculated as explained above

Parameters concerning the natural history of the disease

Number of stages

n	number of stages used to model the latent period
l	number of stages used to model the early infectious period
m	number of stages used to model the (symptomatic) infectious period
j	number of stages used to model convalescence

Sojourn times

D_E	average duration of the incubation period; δ is calculated such that $\delta = n / D_E$ the last l stages are used as early infectious period (average duration: $D_L = D_E\, l / n$)
D_D	average time after onset when a severe case seeks medical help; α is calculated such that $\alpha = 1 / D_D$
$D_{A,a}$	average infectious duration for asymptomatic cases $\gamma_{A,a}$ is calculated such that $\gamma_{A,a} = m / D_{A,a}$
$D_{M,a}$	average infectious duration of moderately sick cases $\gamma_{M,a}$ is calculated such that $\gamma_{M,a} = m / D_{M,a}$
$D_{V,a}$	average duration of infectivity of untreated very or extremely sick cases; $\gamma_{V,a,U}$ is calculated such that $\gamma_{V,a,U} = m / D_{V,a}$
D_C	average duration of convalescence; ρ is calculated such that $\rho = j / D_C$

Course of disease

$c_{a,r}(A)$	fraction of asymptomatic infections (given age a and risk r)
$s_{a,r}$	fraction of severe cases among symptomatic ones
$h_{a,r}$	fraction of severe cases who need hospitalization (unless treated) the fraction of infected cases who - develops moderate disease is $c_{a,r}(M) = \left(1 - s_{a,r}\right)\left(1 - c_{a,r}(M)\right)$ - becomes bed-ridden at home is $c_{a,r}(V) = s_{a,r}\left(1 - h_{a,r}\right)\left(1 - c_{a,r}(M)\right)$ - become extremely severe cases is $c_{a,r}(X) = s_{a,r} h_{a,r}\left(1 - c_{a,r}(M)\right)$
d_a	fraction of untreated extremely severe cases who die; from this, τ_a is chosen such that $d_a = \dfrac{\tau_a}{\tau_a + \gamma_{S,a,U}} \sum_{k=0}^{m-1} \left(\dfrac{\tau_a}{\tau_a + \gamma_{S,a,U}} \right)^k$

Parameters concerning the contagiousness of the infection

b_L	relative contagiousness of cases in the late incubation period
b_A	relative contagiousness of asymptomatic cases
b_M	relative contagiousness of moderately sick cases
b_V	relative contagiousness of severely sick cases
x_{50}	parameter regulating the course of contagiousness

$x_{50} = 1$	only the first stage after onset of disease is contagious
$0.5 < x_{50} < 1$	contagiousness decreases after onset of disease
$x_{50} = 0.5$	equal contagiousness during the whole course of disease
$0 < x_{50} < 0.5$	contagiousness increases after onset of disease

	from this, x is calculated such that $x_{50} = \sum_{i=0}^{m/2} x^{i-1} \Big/ \sum_{i=0}^{m} x^{i-1}$ if m is an even number or $x_{50} = \left(\sum_{i=0}^{(m-1)/2} x^{i-1} + \frac{x^{(m-1)/2+1}}{2} \right) \Big/ \sum_{i=0}^{m} x^{i-1}$ if m is an odd number, respectively
R_0	basic reproduction number; the contact rates $\beta_{L_k,a_s,a_i}(t)$, $\beta_{A_k,a_s,a_i}(t)$, $\beta_{M_k,a_s,a_i}(t)$ and $\beta_{V_k,a_s,a_i}(t)$ are calculated from R_0 and from the contagiousness factors as explained above
$\lambda_a(t)$	force of infection for susceptible individuals of age a at time t (see calculation above)

Parameters concerning contact reduction

r_{iso_M}	fraction of contacts of moderately sick patients that are prevented by partial isolation
r_{iso_V}	fraction of contacts of very sick patients that are prevented by partial isolation
r_{iso_H}	fraction of contacts of hospitalized patients that are prevented by partial isolation
r_{gen}	general fraction of contacts that are prevented at time t
r_{mass}	fraction of contacts among (healthy) adults that are prevented by cancelling events of mass gatherings at time t
r_{sch}	fraction of contacts among (healthy) children of the same age class that occurs in day care centres or schools
F_{HC}	factor by which the contacts between adults and severely sick children increase because of child health care
F_{CC}	factor by which the contacts between adults and children increase when children are taken care off at home because schools are closed

Parameters concerning antiviral treatment

$T_{\max}$	available number of antiviral treatment doses
D_T	time after onset until when antiviral treatment can still be given; the latest infectious stage $m_{a,T}$ during which treatment can be given, is chosen such that $m_{a,T} / \gamma_{V,a,U} \le D_T \le (m_{a,T} + 1) / \gamma_{V,a,U}$
f_V	fraction of severe cases eligible to receive antiviral treatment; treatment will be given only in the user-specified time window and only as long as supplies last: $f_V(t) = \begin{cases} f_V & \text{if } T(t) < T_{\max} \text{ and } t \text{ in treatment window} \\ 0 & \text{otherwise} \end{cases}$

f_X	fraction of extremely severe cases eligible to receive antiviral treatment; treatment will be given only in the user-specified time window and only as long as supplies last: $f_X(t) = \begin{cases} f_X & \text{if } T(t) < T_{\max} \text{ and } t \text{ in treatment window} \\ 0 & \text{otherwise} \end{cases}$
f_D	fraction by which the duration of infectiousness is reduced by antivirals; $\gamma_{V,a,T}$ is calculated from this such that $\gamma_{V,a,T} = m/((1-f_D)D_{V,a})$
f_I	fraction by which the infectiousness of treated cases is reduced by antivirals
f_H	fraction of hospitalizations prevented by antiviral treatment