The impact of prophylaxis of healthcare workers on influenza pandemic burden

Michael Gardam, Dong Liang, Seyed M. Moghadas,
Jianhong Wu, Qingling Zeng, Huaiping Zhu

December 18, 2006

1 The mathematical model

We assumed that the transmission of infection can occur through contacts between susceptible and infected individuals, in which mass action incidence is used for sake of simplicity. Previous work (Arino *et al.*, 2006) shows that this simplification still provides a good approximation to a more realistic situation in which other incidence functions may be used. Since the period of a pandemic is expected to be short, we ignore the effect of birth and natural death rates on the transmission dynamics of infection. It is assumed that infected individuals under treatment can contribute to disease transmission only through contacts with their healthcare providers. Antiviral treatment is assumed to reduce the infectious period and infectiousness of a clinical case from when treatment is initiated (Ferguson *et al.*, 2005, 2003). We considered only susceptible healthcare workers for a prophylactic treatment that reduces susceptibility, infectiousness if infection occurs, and the probability of developing clinical symptoms. These assumptions, with the model structure described in the main paper (Figure 1), lead to the following sets of deterministic equations:

(a) *General population*:

$$\begin{aligned}
S' &= -\beta Q S, \\
E' &= \beta Q S - \mu_{_E} E, \\
A' &= (1-p)\mu_{_E} E - \mu_{_A} A, \\
P' &= p\mu_{_E} E - \mu_{_P} P, \\
I' &= \mu_{_P} P - \mu_{_I} I, \\
I'_{_U} &= (1-\rho)\mu_{_I} I - (\mu_{_U} + d_{_U}) I_{_U}, \\
I'_{_T} &= \rho\mu_{_I} I - (\mu_{_T} + d_{_T}) I_{_T}, \\
R' &= \mu_{_A} A + \mu_{_U} I_{_U} + \mu_{_T} I_{_T},
\end{aligned} \tag{1}$$

(b) *HCWs without prophylaxis*:

$$\begin{aligned}
S'_{H} &= -[\beta Q + \beta_{H} Q_{H}] S_{H}, \\
E'_{H} &= [\beta Q + \beta_{H} Q_{H}] S_{H} - \mu_{E} E_{H}, \\
A'_{H} &= (1-p)\mu_{E} E_{H} - \mu_{A} A_{H}, \\
P'_{H} &= p\mu_{E} E_{H} - \mu_{P} P_{H}, \\
I'_{H} &= \mu_{P} P_{H} - \mu_{I} I_{H}, \\
I'_{HU} &= (1-\rho_{H})\mu_{I} I_{H} - (\mu_{U} + d_{U}) I_{HU}, \\
I'_{HT} &= \rho_{H}\mu_{I} I_{H} - (\mu_{T} + d_{T}) I_{HT}, \\
R'_{H} &= \mu_{A} A_{H} + \mu_{U} I_{HU} + \mu_{T} I_{HT},
\end{aligned} \tag{2}$$

(c) *HCWs with prophylaxis*:

$$\begin{aligned}
S'_{HP} &= -(1-\alpha_{S})[\beta Q + \beta_{H} Q_{H}] S_{HP}, \\
E'_{HP} &= (1-\alpha_{S})[\beta Q + \beta_{H} Q_{H}] S_{HP} - \mu_{E} E_{HP}, \\
A'_{HP} &= (1-p_{P})\mu_{E} E_{HP} - \mu_{A} A_{HP}, \\
P'_{HP} &= p_{P}\mu_{E} E_{HP} - \mu_{P} P_{HP}, \\
I'_{HP} &= \mu_{P} P_{HP} - \mu_{I} I_{HP}, \\
I'_{HPU} &= (1-\rho_{H})\mu_{I} I_{HP} - (\mu_{U} + d_{U}) I_{HPU}, \\
I'_{HPT} &= \rho_{H}\mu_{I} I_{HP} - (\mu_{T} + d_{T}) I_{HPT}, \\
R'_{HP} &= \mu_{A} A_{HP} + \mu_{U} I_{HPU} + \mu_{T} I_{HPT},
\end{aligned} \tag{3}$$

where " $'$ " denotes the derivative with respect to the time,

$$\begin{aligned}
Q &= \delta_{A} A + \delta_{P} P + I + \delta_{U} I_{U} + \delta_{A} A_{H} + \delta_{P} P_{H} + I_{H} + \delta_{U} I_{HU} \\
&\quad + \alpha_{P}(\delta_{A} A_{HP} + \delta_{P} P_{HP} + I_{HP} + \delta_{U} I_{HPU}), \\
Q_{H} &= \delta_{T}(I_{T} + I_{HT} + \alpha_{P} I_{HPT}) + \delta_{A} A_{H} + \delta_{P} P_{H} \\
&\quad + \alpha_{P}(\delta_{A} A_{HP} + \delta_{P} P_{HP}),
\end{aligned}$$

and the parameters are defined as

β: baseline transmission rate in the general population;
β_{H}: baseline transmission rate within the healthcare setting;
μ_{E}: progression rate of exposed to pre-symptomatic infection;
μ_{P}: progression rate of pre-symptomatic to symptomatic infection (stage 1);
μ_{I}: progression rate of stage 1 to stage 2 symptomatic infection;
μ_{A}: recovery rate of asymptomatic infection;
μ_{U}: recovery rate of untreated symptomatic infection;
μ_{T}: recovery rate of treated symptomatic infection;
d_{U}: death rate of untreated symptomatic infection;
d_{T}: death rate of treated symptomatic infection;
δ_{P}: reduction in transmission of pre-symptomatic infection;
δ_{A}: reduction in transmission of asymptomatic infection;

δ_U: reduction in transmission of untreated symptomatic infection;
δ_T: reduction in transmission of treated symptomatic infection;
α_S: reduction in susceptibility due to prophylaxis;
α_P: reduction in infectiousness due to prophylaxis;
p: probability of developing symptoms without prophylaxis;
p_P: probability of developing symptoms with prophylaxis;
ρ: treatment level of the general population;
ρ_H: treatment level of healthcare workers.

An average incubation period ($1/\mu_E$) of 1.25 days (within the estimated range 1.48 ± 0.48 days) is associated with exposed cases (Ferguson *et al.*, 2003), after which infected individuals either develop clinical symptoms or undergo an asymptomatic phase for the entire course of infection. Since influenza can be transmitted before symptoms appear, we considered a relatively short pre-symptomatic infection ($1/\mu_P$) as an extension to previous work (Arino *et al.*, 2006). This is consistent with the assumption made in a recent modeling study for a 0.25-day delay since the onset of clinical symptoms until diagnosis of the infected case (Ferguson *et al.*, 2003). Based on the infectiousness profile (Ferguson *et al.*, 2003), we divided the symptomatic infection into two stages including 1-day period ($1/\mu_I$) for high viral shedding and a period ($1/\mu_U$) of 2.85 days for low viral shedding. This corresponds to a mean infectiousness period of 4.1 days (including pre-symptomatic stage) for the clinical infection (Ferguson *et al.*, 2005, 2003; Longini *et al.*, 2004, 2005). We used the same infectious period ($1/\mu_A$) for the asymptomatic infection. It is assumed that stage 1 symptomatic infection provides the window of opportunity for an effective treatment with maximum response of infected individuals to antiviral drugs. Antiviral treatment is assumed to reduce the infectious period ($1/\mu_T$) by 1.5 days, and infectiousness by 60% from when treatment is initiated (Ferguson *et al.*, 2005, 2003). Prophylactic treatment of healthcare workers is assumed to reduce susceptibility to infection by 30%, infectiousness if infection occurs by 60%, and the probability of developing clinical symptoms by 65% (Ferguson *et al.*, 2005, 2003).

Since the transmission rate within healthcare settings is influenced by the presence of asymptomatically (or even clinically) infected HCWs, susceptible HCWs may be exposed to even higher level of exposure (Low & Wilder-Smith, 2005; Nguyen-Van-Tam et al., 1999). This explains the appearance of the terms A_H, P_H, A_{HP} and P_{HP} in the force of infection Q_H. Parameters for the level of treatment, as explained in the main paper, depend on the availability of HCWs at time t. Let ν and ν_H represent the fractions of clinical cases in the GP and HCWs, respectively, which are effectively treated within a naïve healthcare system. We define $\rho = \theta\nu$ and $\rho_H = \theta\nu_H$ where θ is given by the expression (4) in the main paper. The parameter $\theta(t)$ represents the proportion of HCWs who provide care at time t during a pandemic (including susceptible, exposed, asymptomatic, pre-symptomatic, and recovered individuals), except those who are infected and clinically recognizable.

Thus, at the onset of epidemic, $\theta = 1$ and the treatment parameters reduce to $\rho = \nu$ and $\rho_{_H} = \nu_{_H}$. For the purpose of simulations, we assumed that 90% of clinical cases in the GP (60% of infections) and 100% of those among HCWs are detected and effectively treated (Ferguson *et al.*, 2003), corresponding to $\nu = 0.9$ and $\nu_{_H} = 1$, when infection is introduced into the population.

2 Control reproduction number

Here, we will treat parameters ρ and $\rho_{_H}$ as constants by considering $\theta = 1$, which is sufficient for the calculation of the control reproduction number. This calculation involves the linearization of the model at the disease free equilibrium, which coincides with the original model when $\rho = \nu$ and $\rho_{_H} = \nu_{_H}$ are constants. Also, our need for the final size equation is to establish a relationship between the basic (or control) reproduction number and the final size of the susceptible population when the epidemic dies out. For this purpose, it again suffices to assume constant treatment levels.

We may follow a previous approach (van den Driessche & Watmough, 2002) to calculate the control reproduction number ($\mathscr{R}_c$). We first simplify the model by introducing new change of variables as follows:

$$x = \begin{bmatrix} S \\ S_{_H} \\ S_{_{HP}} \end{bmatrix}, \quad y = \begin{bmatrix} E \\ E_{_H} \\ E_{_{HP}} \end{bmatrix}, \quad z_{_P} = \begin{bmatrix} P \\ P_{_H} \\ P_{_{HP}} \end{bmatrix}, \quad z_{_A} = \begin{bmatrix} A \\ A_{_H} \\ A_{_{HP}} \end{bmatrix},$$

$$i = \begin{bmatrix} I \\ I_{_H} \\ I_{_{HP}} \end{bmatrix}, \quad i_{_U} = \begin{bmatrix} I_{_U} \\ I_{_{HU}} \\ I_{_{HPU}} \end{bmatrix}, \quad i_{_T} = \begin{bmatrix} I_{_T} \\ I_{_{HT}} \\ I_{_{HPT}} \end{bmatrix},$$

and

$$f(x, y, z_{_P}, z_{_A}, i, i_{_U}, i_{_T}) = \begin{bmatrix} \beta Q S \\ (\beta Q + \beta_{_H} Q_{_H}) S_{_H} \\ \alpha_{_S} (\beta Q + \beta_{_H} Q_{_H}) S_{_{HP}} \end{bmatrix}.$$

Then the model (1)-(3) can be written as the following system of equations

$$\begin{aligned} x' =& - f(x, y, z_{_P}, z_{_A}, i, i_{_U}, i_{_T}), \\ y' =& f(x, y, z_{_P}, z_{_A}, i, i_{_U}, i_{_T}) - V_{_E} y, \\ z'_{_P} =& V_{_{EP}} y - V_{_P} z_{_P}, \\ z'_{_A} =& V_{_{EA}} y - V_{_A} z_{_A}, \\ i' =& V_{_P} z_{_P} - V_{_I} i, \\ i'_{_U} =& V_{_U} i - V_{_{IU}} i_{_U}, \\ i'_{_T} =& V_{_T} i - V_{_{IT}} i_{_T}, \end{aligned} \tag{4}$$

where

$$V_{_E} = \mu_{_E}\mathbb{I}; \quad V_{_P} = \mu_{_P}\mathbb{I}; \quad V_{_A} = \mu_{_A}\mathbb{I}; \quad V_{_I} = \mu_{_I}\mathbb{I}; \quad V_{_{IU}} = (\mu_{_U} + d_{_U})\mathbb{I};$$
$$V_{_{IT}} = (\mu_{_T} + d_{_T})\mathbb{I}; \quad V_{_{EP}} = V_{_E} - V_{_{EA}}; \quad V_{_U} = V_{_I} - V_{_T};$$
$$V_{_{EA}} = \mu_{_E}\begin{bmatrix} 1-p & 0 & 0 \\ 0 & 1-p & 0 \\ 0 & 0 & 1-p_{_P}, \end{bmatrix}; \quad V_{_T} = \mu_{_I}\begin{bmatrix} \rho & 0 & 0 \\ 0 & \rho_{_H} & 0 \\ 0 & 0 & \rho_{_H} \end{bmatrix},$$

and $\mathbb{I}$ is the identity matrix of size 3×3. Let $X = [S, S_{_H}, \alpha_{_S} S_{_{HP}}]^t$ and $Y = [0, S_{_H}, \alpha_{_S} S_{_{HP}}]^t$. We now define square matrices F and V as

$$F = \begin{bmatrix} F_{_E} & F_{_P} & F_{_A} & F_{_I} & F_{_{IU}} & F_{_{IT}} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} V_{_E} & 0 & 0 & 0 & 0 & 0 \\ -V_{_{EP}} & V_{_P} & 0 & 0 & 0 & 0 \\ -V_{_{EA}} & 0 & V_{_A} & 0 & 0 & 0 \\ 0 & -V_{_P} & 0 & V_{_I} & 0 & 0 \\ 0 & 0 & 0 & -V_{_U} & V_{_{IU}} & 0 \\ 0 & 0 & 0 & -V_{_T} & 0 & V_{_{IT}} \end{bmatrix},$$

where $F_{_E} = O_{3\times 3}$ zero matrix, and

$$\begin{aligned} F_{_P} &= \beta X \begin{bmatrix} 1 & 1 & \alpha_{_P} \end{bmatrix} \delta_{_P} + \beta_{_H} Y \begin{bmatrix} 0 & 1 & \alpha_{_P} \end{bmatrix} \delta_{_P}, \\ F_{_A} &= \beta X \begin{bmatrix} 1 & 1 & \alpha_{_P} \end{bmatrix} \delta_{_A} + \beta_{_H} Y \begin{bmatrix} 0 & 1 & \alpha_{_P} \end{bmatrix} \delta_{_A}, \\ F_{_I} &= \beta X \begin{bmatrix} 1 & 1 & \alpha_{_P} \end{bmatrix}, \\ F_{_{IU}} &= \beta X \begin{bmatrix} 1 & 1 & \alpha_{_P} \end{bmatrix} \delta_{_U}, \\ F_{_{IT}} &= \beta_{_H} Y \begin{bmatrix} 1 & 1 & \alpha_{_P} \end{bmatrix} \delta_{_T}. \end{aligned}$$

Then, the control reproduction number is the spectral radius of the matrix FV^{-1} (van den Driessche & Watmough, 2002). Without prophylactic treatment, and considering HCWs in the general population, we have

$$F = \beta S_0 \begin{bmatrix} 0 & \delta_{_P} & \delta_{_A} & 1 & \delta_{_U} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} \mu_{_E} & 0 & 0 & 0 & 0 & 0 \\ -p\mu_{_E} & \mu_{_P} & 0 & 0 & 0 & 0 \\ -(1-p)\mu_{_E} & 0 & \mu_{_A} & 0 & 0 & 0 \\ 0 & -\mu_{_P} & 0 & \mu_{_I} & 0 & 0 \\ 0 & 0 & 0 & -(1-\rho)\mu_{_I} & \mu_{_U} + d_{_U} & 0 \\ 0 & 0 & 0 & -\rho\mu_I & 0 & \mu_{_T} + d_{_T} \end{bmatrix}.$$

A simple calculation yields the following expression

$$\mathscr{R}_c = \beta S_0 \Big(\frac{(1-p)\delta_{_A}}{\mu_{_A}} + \frac{p\delta_{_P}}{\mu_{_P}} + \frac{p}{\mu_{_I}} + \frac{p(1-\rho)\delta_{_U}}{\mu_{_U}+d_{_U}} \Big). \tag{5}$$

In the absence of antiviral treatment ($\rho = 0$), $\mathscr{R}_c$ reduces to the expression (5) in the main paper for the basic reproduction number.

3 Final size relation

At the beginning of the epidemic, we assume that

$$S(0) + S_{_H}(0) + S_{_{HP}}(0) + I(0) + I_{_H}(0) + I_{_{HP}}(0) = C,$$

and other variables are zero, leading to

$$y(0) = z_{_P}(0) = z_{_A}(0) = i_{_U}(0) = i_{_T}(0) = 0.$$

For simplicity, we denote $\lim_{t\to\infty} g(t)$ and $\int_0^\infty g(s)ds$ by $g(\infty)$ and $\hat{g}$, respectively, for any non-negative integrable function g defined on the interval $0 \le t \le \infty$. It can be easily shown that all compartments of exposed, pre-symptomatic, symptomatic (treated or untreated), and asymptomatic infection tend to 0 as $t \to \infty$. Integrating $i'_{_T}$, $i'_{_U}$, i', $z'_{_A}$ and $z'_{_P}$ of the model (4) leads to

$$\begin{aligned}
\hat{i}_{_T} &= V_{_{IT}}^{-1} V_{_T} \hat{i}, && (6)\\
\hat{i}_{_U} &= V_{_{IU}}^{-1} V_{_U} \hat{i}, && (7)\\
\hat{i} &= V_{_I}^{-1} V_{_P} \hat{z}_{_P} + V_{_I}^{-1} i(0), && (8)\\
\hat{z}_{_A} &= V_{_A}^{-1} V_{_{EA}} \hat{y}, && (9)\\
\hat{z}_{_P} &= V_{_P}^{-1} V_{_{EP}} \hat{y}, && (10)
\end{aligned}$$

Also, integrating the sum of x' and y' gives $\hat{y} = V_{_E}^{-1}(x(0) - x(\infty))$, and hence

$$\begin{aligned}
\hat{z}_{_P} &= V_{_P}^{-1} V_{_{EP}} V_{_E}^{-1} (x(0) - x(\infty)), && (11)\\
\hat{z}_{_A} &= V_{_A}^{-1} V_{_{EA}} V_{_E}^{-1} (x(0) - x(\infty)), && (12)\\
\hat{i} &= V_{_I}^{-1} V_{_{EP}} V_{_E}^{-1} (x(0) - x(\infty)) + V_{_I}^{-1} i(0), && (13)
\end{aligned}$$

Letting

$$\begin{aligned}
W_1 &= \begin{bmatrix} 1 & 0 & 0 \end{bmatrix} \Big(\delta_{_P} V_{_P}^{-1} V_{_{EP}} + \delta_{_A} V_{_A}^{-1} V_{_{EA}} + V_{_I}^{-1} V_{_{EP}} + \delta_{_U} V_{_{IU}}^{-1} V_{_U} V_{_I}^{-1} V_{_{EP}} \Big) V_{_E}^{-1},\\
W_2 &= \begin{bmatrix} 0 & 1 & \alpha_{_P} \end{bmatrix} \Big(\delta_{_P} V_{_P}^{-1} V_{_{EP}} + \delta_{_A} V_{_A}^{-1} V_{_{EA}} + V_{_I}^{-1} V_{_{EP}} + \delta_{_U} V_{_{IU}}^{-1} V_{_U} V_{_I}^{-1} V_{_{EP}} \Big) V_{_E}^{-1},\\
W_3 &= \begin{bmatrix} 1 & 0 & 0 \end{bmatrix} \Big(1 + \delta_{_U} V_{_{IU}}^{-1} V_{_U} \Big) V_{_I}^{-1} i(0),\\
W_4 &= \begin{bmatrix} 0 & 1 & \alpha_{_P} \end{bmatrix} \Big(1 + \delta_{_U} V_{_{IU}}^{-1} V_{_U} \Big) V_{_I}^{-1} i(0),\\
W_5 &= \begin{bmatrix} 0 & 1 & \alpha_{_P} \end{bmatrix} \Big(\delta_{_P} V_{_P}^{-1} V_{_{EP}} + \delta_{_A} V_{_A}^{-1} V_{_{EA}} + \delta_{_T} V_{_{IT}}^{-1} V_{_T} V_{_I}^{-1} V_{_{EP}} \Big) V_{_E}^{-1},\\
W_6 &= \begin{bmatrix} 1 & 1 & \alpha_{_P} \end{bmatrix} \delta_{_T} V_{_{IT}}^{-1} V_{_T} V_{_I}^{-1} i(0),
\end{aligned}$$

it follows from (6)-(13) that

$$\begin{aligned}\hat{Q} &= (W_1 + W_2)(x(0) - x(\infty)) + W_3 + W_4,\\ \hat{Q}_{_H} &= W_5(x(0) - x(\infty)) + W_6,\end{aligned}$$

Integrating the equations for S', $S'_{_H}$ and $S'_{_{HP}}$ gives

$$\log S(0) - \log S(\infty) = \int_0^\infty \beta Q(t)dt = \beta\hat{Q}, \tag{14}$$

$$\log S_{_H}(0) - \log S_{_H}(\infty) = \int_0^\infty \beta Q(t)dt + \int_0^\infty \beta_{_H} Q_{_H} dt = \beta\hat{Q} + \beta_{_H}\hat{Q}_{_H}, \tag{15}$$

and

$$\begin{aligned}\log S_{_{HP}}(0) - \log S_{_{HP}}(\infty) &= \int_0^\infty \beta\alpha_{_S} Q(t)dt + \int_0^\infty \beta_{_H}\alpha_{_S} Q_{_H} dt &(16)\\ &= \alpha_{_S}\big(\log S_{_H}(0) - \log S_{_H}(\infty)\big), &(17)\end{aligned}$$

which lead to a relationship between the initial and final sizes of the susceptible HCWs with and without prophylaxis as

$$\frac{S_{_{HP}}(\infty)}{S_{_{HP}}(0)} = \Big(\frac{S_{_H}(\infty)}{S_{_H}(0)}\Big)^{(1-\alpha_{_S})}. \tag{18}$$

The above equations in (14), (15) and (18) can be used to evaluate $S(\infty)$, $S_{_H}(\infty)$ and $S_{_{HP}}(\infty)$ in terms of the model parameters, and determine the values of $\hat{y}$, $\hat{z}_{_P}$, $\hat{z}_{_A}$, $\hat{i}$, $\hat{i}_{_U}$ and $\hat{i}_{_T}$.

In the general population, assuming that W_3 is small enough to be neglected, the final size relation is given by

$$\log\frac{S_0}{S_\infty} = \frac{\mathscr{R}_c}{S_0}(S_0 - S_\infty), \tag{19}$$

where $\mathscr{R}_c$ is defined in (5) and S_∞ is the size of susceptible population when the epidemic dies out (Arino *et al.*, 2006). In the absence of antiviral treatment, this relation reduces to (6) in the main paper, which allows us to calculate $\mathscr{R}_0$ from the assumed attack rate $p(1 - S_\infty/S_0)$. For the particular case of 30% clinical attack rate in the general population, it follows that $S_\infty/S_0 = 0.5522$, assuming that 67% of infected individuals develops clinical symptoms. Taking into account equation (6) in the main paper, we obtain the value of $\mathscr{R}_0 = 1.3261$. Thus, with the parameter values given in Table 1 of the main paper, the expression for $\mathscr{R}_0$ provides an estimation of $\beta = 1.2214/S_0$ for the baseline transmission rate of infection. We used the final size relation to estimate a range of β according to a range of $25\% - 35\%$ clinical attack rate in the GP. To determine the transmission rate in the healthcare setting, we ran the simulations (given β for the GP) in the absence of treatment

and prophylaxis, in order to estimate values of $\beta_{_H}$ that correspond to a range of attack rates among HCWs given by the relation $p(1 - S_\infty/S_0)$. Using S_∞ and S_0 for HCWs, and assuming attack rates of 30% and 45% in the GP and HCWs, respectively, simulations provide an estimation of $\beta_{_H} = 4.9845/\big(S_{_H}(0) + S_{_{HP}}(0)\big)$.

We used the estimated ranges of β and $\beta_{_H}$ for performing an uncertainty analysis of the model with a range of $25\% - 35\%$ for the reduction in susceptibility due to prophylaxis ($\alpha_{_S}$). With the parameter values given in Table 1, we run the simulations for samples generated by the LHS technique to calculate 1000 values of the averaged control reproduction number ($\mathscr{R}_a$) using the final size relation (19), as prophylaxis coverage of HCWs increases. Box plots in Figure 3 of the main paper provide a range of variations in $\mathscr{R}_a$ according to the changes in the clinical attack rates and susceptibility of HCWs with prophylaxis. Figure 4 in the main paper shows the ranges of variations in the total number of clinical infections and deaths during the entire course of an outbreak. Our analysis shows that the predicted outbreak dynamics is substantially affected by transmission rates; and the effectiveness of healthcare worker prophylaxis reduces as these rates increase.

References

Arino, J., Brauer, F., van den Driessche, P., Watmough J., Wu, J. Simple models for containment of a pandemic, *J R Soc Interf* 2006, published on line.

Ferguson, N.M., Cummings, D.A.T, Cauchemez, S., Fraser, C., Riley, S., Meeyai, A., Iamsirithaworn, S., Burke, D.S. 2005, Strategies for containing an emerging influenza pandemic in Southeast Asia, Nature 437, 209-214.

Ferguson, N.M., Mallett, S., Jackson, H., Roberts, N., Ward, P. 2003, A population-dynamic model for evaluating the potential spread of drug-resistant influenza virus infections during community-based use of antivirals, J. Antimicrob. Chemother. 51, 977-990.

Longini, Jr., I.M., Halloran, M.E., Nizam, A., Yang, Y. 2004, Containing pandemic influenza with antiviral agents, Am. J. Epidemiol. 159, 623-633.

Longini Jr., I.M., Nizam, A., Xu, S., Ungchusak, K., Hanshaoworakul, W., Cummings, D.A.T., Halloran, M.E. 2005, Containing pandemic influenza at the source, Science 309, 1083-1087.

Low, J.G.H., Wilder-Smith, A. Infectious respiratory illnesses and their impact on healthcare workers: a review, *Ann Acad Med* 2005; 34: 105-10.

Nguyen-Van-Tam, J., Granfield, R., Pearson, J., Fleming, D., Keating, N. Do influenza epidemics affect patterns of sickness absence among British hospital staff? *Infect Control Hosp Epidemiol* 1999; 20: 691-94.

van den Driessche, P., Watmough, J. 2002, Reproduction numbers and subthreshold endemic equilibria for compartmental models of disease transmission, Math. Biosc. 180, 29-48.