

# The impact of prophylaxis of healthcare workers on influenza pandemic burden

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Several models have rationalized the use of antiviral drugs as an early control measure for delaying the progression and limiting the size of outbreaks during an influenza pandemic. However, the strategy for use of these drugs is still under debate. We evaluated the impact of prophylaxis of healthcare workers (HCWs) through a mathematical model that considers attack rates in a range of 25–35% in the general population and 25–50% among HCWs. Simulations and uncertainty analysis using the demographics of the province of Ontario, Canada show that increasing prophylaxis coverage of HCWs has little impact on reducing the reproduction number of disease transmission and may not prevent the occurrence of an outbreak if expected. However, it does enable a high level of treatment, which substantially reduces morbidity and mortality in the population as a whole. Therefore, prophylaxis of HCWs should be considered an important part of public health efforts for minimizing influenza pandemic burden and its socio-economic disruption.

**Keywords:** influenza pandemic; antivirals; prophylactic treatment; epidemic models

## 1. INTRODUCTION

Previous influenza pandemics occurred with significant rates of morbidity and mortality worldwide (Cox *et al.* 2003; Taubenberger & Morens 2006). Such a high mortality is often attributed to the lack of pre-existing immunity to a mutated virus that has transferred to the human populations (Nicholson *et al.* 2003; Hoft & Belshe 2004). Recent outbreaks of highly pathogenic avian influenza in poultry have raised the threat of an impending influenza pandemic through the mutation of the avian virus into one that readily infects humans (Gani *et al.* 2005).

Planning for the next influenza pandemic may be influenced by several public health intervention strategies that aim to reduce morbidity and mortality, as well as socio-economic devastation. Although vaccination has been a key strategy for interpandemic influenza epidemics (WHO 2000), it may not be the primary control measure early on in a pandemic (Ferguson *et al.* 2003). Other public health measures,

including social distancing, school/border closure, travel restrictions and quarantine/isolation, may be considered; however, these measures, in general, have limited impact on mitigating the pandemic and, in some cases, may not even be feasible (Ferguson *et al.* 2006). Therefore, antiviral agents are widely considered to be an important control strategy for both treatment and prophylaxis during a pandemic (Ferguson *et al.* 2003, 2005; Longini *et al.* 2004, 2005; Gani *et al.* 2005).

One plausible treatment strategy would be to focus primarily on the treatment of hospitalized patients, healthcare workers (HCWs) and first responders. An extended programme could also include prophylaxis of HCWs, which would require stockpiling massive quantities of antivirals to be taken for the duration of a pandemic. These strategies lead to subtle, yet very significant, policy differences. While recognizing that the extended programme attempts to maintain high capacity in the healthcare system, it may entail a prohibitively expensive public health policy. Therefore, solid analysis and computer-assisted simulations should be undertaken to predict the trade-off between financial cost and overall healthcare benefit before implementing this strategy.

In the presence of antiviral agents, it is imperative to assess the relative impact of treatment of priority

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groups and prophylaxis of HCWs on preventing morbidity and mortality in the population as a whole. Assuming a viral strain with 25–35% clinical attack rate over the estimated 8–12 weeks of a pandemic wave (Longini *et al.* 2004, 2005; Gani *et al.* 2005), a sizable portion of HCWs may become infected early on, due to a higher level of exposure while providing care (Salgado *et al.* 2002; Bridges *et al.* 2003; Horcajada *et al.* 2003; Low & Wilder-Smith 2005). This will reduce the capacity of the healthcare system, which in turn could compromise the effectiveness of any treatment strategy. The prompt onset of treatment can substantially contribute to the containment of a pandemic, by reducing both the infectivity and the period of infectiousness of clinical cases. With a diminished healthcare work force in place and inadequate level of treatment, the disease can readily spread in the population. One would therefore expect that prophylaxis of HCWs may alleviate this situation by reducing the risk of infection and absenteeism due to illness as well as concern over exposure to infection in the workplace (Cinti *et al.* 2005).

This study undertakes to evaluate the relative importance of prophylaxis and treatment for a pandemic influenza, using population demographics of the province of Ontario, Canada as a case study. Here, we develop a mathematical model that incorporates parameters representing the effect of treatment and the functional relation describing the effect of prophylaxis of HCW on disease burden.

## 2. THE MODEL STRUCTURE

Following previous work (Arino *et al.* 2006), we considered a relatively homogeneous population consisting of HCWs and the rest of the population as a general population (GP). We further divided each subpopulation into several compartments comprising susceptible ( $S$ ), exposed but not infectious ( $E$ ), asymptomatic and infectious ( $A$ ), pre-symptomatic and infectious ( $P$ ), symptomatic and highly infectious (stage 1,  $I$ ), untreated symptomatic and infectious (stage 2,  $I_U$ ), treated symptomatic and infectious ( $I_T$ ), recovered ( $R$ ) and dead ( $D$ ) individuals (figure 1). These compartments are denoted by using subindex  $H$  ( $HP$ ) for the subpopulation of HCWs without or with prophylaxis.

We assumed that the transmission of infection can occur through contacts between the susceptible and infected individuals, in which mass action incidence is used for the 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. Therefore, under restricted infection control practices (Salgado *et al.* 2002), hospitalized patients

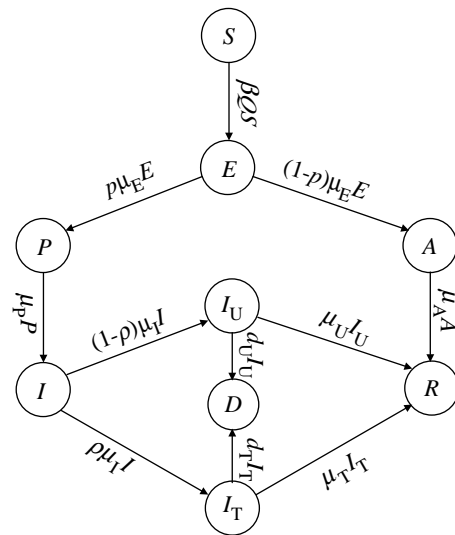


Figure 1. A model diagram with treatment strategy.

are assumed to have contacts with only HCWs during their hospitalization. We considered only susceptible HCWs for a prophylactic treatment that reduces susceptibility, infectiousness if infection occurs and the probability of developing clinical symptoms. These assumptions, with the associated parameters given in table 1, lead to the following sets of deterministic equations:

### 2.1. General population

$$\begin{aligned}
 S' &= -\beta QS, \\
 E' &= \beta QS - \mu_E E, \\
 A' &= (1-p)\mu_E E - \mu_A A, \\
 P' &= p\mu_E E - \mu_P P, \\
 I' &= \mu_P P - \mu_I I, \\
 I'_U &= (1-\rho)\mu_I I - (\mu_U + d_U)I_U, \\
 I'_T &= \rho\mu_I I - (\mu_T + d_T)I_T, \\
 R' &= \mu_A A + \mu_U I_U + \mu_T I_T,
 \end{aligned} \tag{2.1}$$

### 2.2. Healthcare workers without prophylaxis

$$\begin{aligned}
 S'_H &= -[\beta Q + \beta_H Q_H]S_H, \\
 E'_H &= [\beta Q + \beta_H Q_H]S_H - \mu_E E_H, \\
 A'_H &= (1-p)\mu_E E_H - \mu_A A_H, \\
 P'_H &= p\mu_E E_H - \mu_P P_H, \\
 I'_H &= \mu_P P_H - \mu_I I_H, \\
 I'_{HU} &= (1-\rho_H)\mu_I I_H - (\mu_U + d_U)I_{HU}, \\
 I'_{HT} &= \rho_H\mu_I I_H - (\mu_T + d_T)I_{HT}, \\
 R'_H &= \mu_A A_H + \mu_U I_{HU} + \mu_T I_{HT},
 \end{aligned} \tag{2.2}$$

Table 1. Description of the model parameters with their values (ranges) for the GP and the HCWs (Salgado *et al.* 2002; Bridges *et al.* 2003; Ferguson *et al.* 2003, 2005; Horcajada *et al.* 2003; Longini *et al.* 2004, 2005; Gani *et al.* 2005; Low & Wilder-Smith 2005; Arino *et al.* 2006; Jefferson *et al.* 2006).

parameter	description	value (range)
$c_1$	clinical attack rate in the GP	25–35%
$c_2$	clinical attack rate among HCWs	25–50%
$1/\mu_E$	incubation period	1.25 days
$1/\mu_P$	infectious period of pre-symptomatic case	0.25 day
$1/\mu_I$	infectious period of symptomatic case (stage 1)	1 day
$1/\mu_U$	infectious period of untreated symptomatic case (stage 2)	2.85 days
$1/\mu_T$	infectious period of treated symptomatic case	1.35 days
$1/\mu_A$	infectious period of asymptomatic case	4.1 days
$d_U$	death rate of untreated symptomatic infection	$0.002 \text{ d}^{-1}$
$d_T$	death rate of treated symptomatic infection	$0.001 \text{ d}^{-1}$
$\delta_P$	reduction in infectiousness of pre-symptomatic case	0.286
$\delta_A$	reduction in infectiousness of asymptomatic case	0.071
$\delta_U$	reduction in infectiousness of untreated symptomatic case	0.143
$\delta_T$	reduction in infectiousness of treated symptomatic case	60%
$\alpha_S$	reduction in susceptibility due to prophylaxis	25–35%
$\alpha_P$	reduction in infectiousness due to prophylaxis	60%
$p$	probability of developing symptoms without prophylaxis	0.67
$p_P$	probability of developing symptoms with prophylaxis	0.35

### 2.3. Healthcare workers with prophylaxis

$$\begin{aligned}
 S'_{HP} &= -(1 - \alpha_S)[\beta_Q Q + \beta_H Q_H]S_{HP}, \\
 E'_{HP} &= (1 - \alpha_S)[\beta_Q Q + \beta_H Q_H]S_{HP} - \mu_E E_{HP}, \\
 A'_{HP} &= (1 - p_P)\mu_E E_{HP} - \mu_A A_{HP}, \\
 P'_{HP} &= p_P \mu_E E_{HP} - \mu_P P_{HP}, \\
 I'_{HP} &= \mu_P P_{HP} - \mu_I I_{HP}, \\
 I'_{HPU} &= (1 - \rho_H)\mu_I I_{HP} - (\mu_U + d_U)I_{HPU}, \\
 I'_{HPT} &= \rho_H \mu_I I_{HP} - (\mu_T + d_T)I_{HPT}, \\
 R'_{HP} &= \mu_A A_{HP} + \mu_U I_{HPU} + \mu_T I_{HPT},
 \end{aligned}
 \tag{2.3}$$

where the prime denotes the derivative with respect to the time, and the equations for the force of infection are given by

$$\begin{aligned}
 Q &= \delta_A A + \delta_P P + I + \delta_U I_U + \delta_A A_H + \delta_P P_H + I_H \\
 &\quad + \delta_U I_{HU} + \alpha_P(\delta_A A_{HP} + \delta_P P_{HP} + I_{HP} + \delta_U I_{HPU}), \\
 Q_H &= \delta_T(I_T + I_{HT} + \alpha_P I_{HPT}) + \delta_A A_H + \delta_P P_H \\
 &\quad + \alpha_P(\delta_A A_{HP} + \delta_P P_{HP}).
 \end{aligned}$$

In comparison with  $Q$ , the force of infection term  $Q_H$  includes the infectious compartments  $I_T$ ,  $I_{HT}$  and  $I_{HPT}$  that correspond to the additional risk of HCWs infection from influenza patients under treatment. The term  $Q_H$  also involves  $A_H$ ,  $P_H$ ,  $A_{HP}$  and  $P_{HP}$ , as evidence shows that many affected HCWs with subclinical or even full clinical syndromes continue to report to work while unwell and become a source of viral shedding (Weingarten *et al.* 1989; Elder *et al.* 1996; Low & Wilder-Smith 2005). Therefore, susceptible HCWs may be exposed to even higher level of influenza transmission (Nguyen-Van-Tam *et al.*

Table 2. (a) The number of HCWs confirmed by the Emergency Management Unit of the Ministry of Health and Long-Term Care in the province of Ontario, Canada, 2004. (b) Population size of Ontario, 2004, represented by Statistics Canada.

	number
(a) healthcare workers	
LPNs (licensed practical nurses)	23 705
active physicians	21 793
RNs (registered nurses)	87 329
RRTs (registered respiratory therapists)	2198
(b) population size	
	12 407 300

1999; Low & Wilder-Smith 2005). More details of the model formulation and parameter assignment can be found in the electronic supplementary material.

The central role of HCWs in a pandemic response may be well represented through maintaining the quality of healthcare and providing high level of treatment. This is affected by several factors including the capacity of the healthcare system at the onset of a pandemic and, more importantly, the proportion of HCWs who are permitted (under the infection control protocol) to contribute to the treatment strategy. We defined the level of treatment ( $\rho$ ) as the product of the fraction of clinical cases in the GP, which is effectively treated ( $\nu$ ), and the proportion of HCWs who provide care during a pandemic ( $\theta$ ). This variable proportion is given by

$$\begin{aligned}
 \theta(t) &= \{S_H + S_{HP} + E_H + E_{HP} + A_H + A_{HP} + P_H \\
 &\quad + P_{HP} + R_H + R_{HP}\}(t) / \{S_H(0) + S_{HP}(0)\},
 \end{aligned}
 \tag{2.4}$$

where  $S_H(0) + S_{HP}(0)$  is the population size of susceptible HCWs (without and with prophylaxis) at the onset of a pandemic. The numerator of this proportion

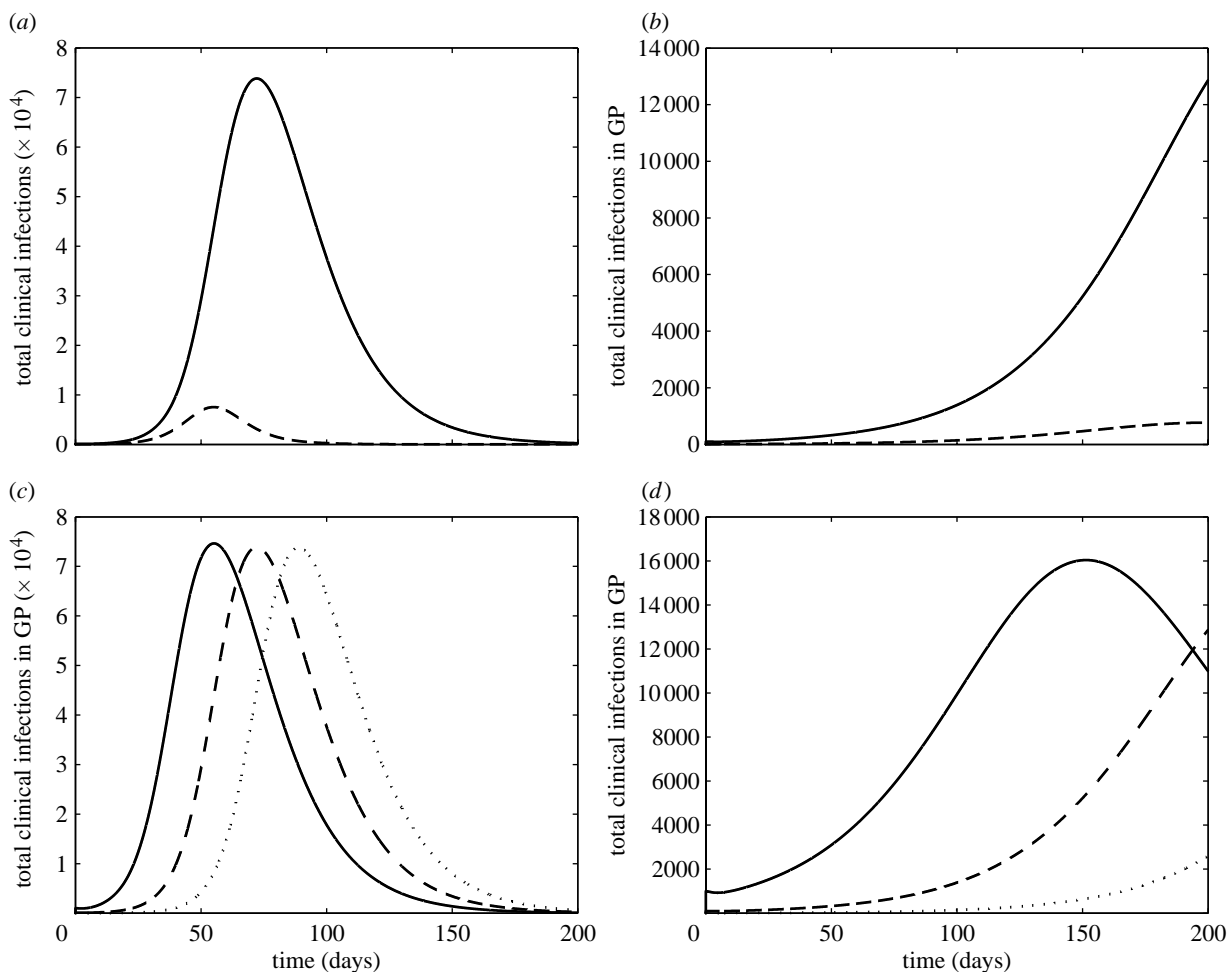


Figure 2. The time courses of the total clinical infections in the GP (solid curves) and HCWs (dashed curves) with 30 and 45% attack rates, respectively, are illustrated in the following: (a) without prophylaxis of HCWs and (b) with 100% prophylaxis coverage of HCWs and 30% reduction in susceptibility due to prophylaxis ( $\alpha_S = 0.3$ ). An initial number of  $I(0) = 100$  infectives in the GP was assumed in (a) and (b). The time courses of the total clinical infections in the GP with different initial values of infectives are illustrated in the following: (c) without prophylaxis and (d) with 100% prophylaxis coverage of HCWs. The initial values of infectives are as follows: dotted curves,  $I(0) = 10$ ; dashed curves,  $I(0) = 100$ ; solid curves,  $I(0) = 1000$ .

includes susceptible, exposed, asymptomatic, pre-symptomatic and recovered HCWs, except those who are infected and clinically recognizable. At the beginning of a pandemic,  $\theta(0) = 1$ , representing the highest level of treatment afforded by the capacity of the healthcare system. However, the spread of infection increases the number of clinical cases among HCWs, thereby reducing their availability as expressed by  $\theta$ . This in turn decreases the level of treatment  $\rho = \nu\theta$ , and also contributes to the GP infection through regular contacts with HCWs outside the workplace.

### 3. BASIC REPRODUCTION NUMBER AND FINAL SIZE RELATION

The number of new infections produced by a single infected individual ( $\mathcal{R}_0$ ) is the product of three parameters: the number of contacts with susceptible individuals per unit time; the probability of viral transmission; and the generation time. In the absence of antiviral treatment, we may follow a previous approach (Diekmann & Heesterbeek 2000; van den Driessche & Watmough 2002) to compute the basic reproduction

number (see electronic supplementary material)

$$\mathcal{R}_0 = \beta S_0 \left( \frac{(1-p)\delta_A}{\mu_A} + \frac{p\delta_P}{\mu_P} + \frac{p}{\mu_I} + \frac{p\delta_U}{\mu_U + d_U} \right), \quad (3.1)$$

where  $\beta$  is the transmission rate;  $S_0$  is the initial size of the susceptible population; and other parameters are defined in table 1. Assuming that, at the beginning of a pandemic, the size of the infected population is small when compared with that of the susceptible population, there is a final size relation

$$\log_e(S_0/S_\infty) = \mathcal{R}_0(1 - S_\infty/S_0), \quad (3.2)$$

where  $S_\infty$  is the size of the susceptible population when the epidemic dies out. To estimate  $\mathcal{R}_0$  from (3.2), we used the clinical attack rate defined as the fraction of the susceptible population that develops clinical symptoms. With the above notation, this rate is given by  $p(1 - S_\infty/S_0)$ . For a range of 25–35% clinical attack rate in the GP, and assuming that 67% of the infected individuals develop clinical symptoms (Longini *et al.* 2004, 2005), the basic reproduction number ranges from 1.2516 to 1.4146 (table 3). However, if the probability of developing clinical symptoms is reduced to 50% (Ferguson *et al.* 2005), then for the same range of clinical attack rates  $\mathcal{R}_0$  will be higher, varying between 1.3863 and 1.7200.

Given the clinical attack rate, the expression for  $\mathcal{R}_0$  provides an estimation of the transmission rate  $\beta$  in the GP (see electronic supplementary material). The clinical attack rate of a pandemic strain may be as high as 60% among those caring for patients with influenza (Salgado *et al.* 2002; Bridges *et al.* 2003; Horcajada *et al.* 2003; Low & Wilder-Smith 2005), and we considered a range of 25–50% attack rate among HCWs. This is reflected in the transmission rate within healthcare settings, which is influenced by the transmission rate in the GP and calculated through the final size relation. With the variations in attack rates, we assessed the effect of changes in the treatment level on the time courses of infection and disease burden.

#### 4. RESULTS

We assumed that, at the onset of a pandemic, 90% of clinical cases in the GP (60% of the total GP infections) and 100% of clinical cases among HCWs are detected and effectively treated (Ferguson *et al.* 2005), corresponding to  $\nu=0.9$  and  $\nu_H=1$ . The results are presented here using parameter values from recently published literature (table 1) and the population demographics of the province of Ontario, Canada (table 2).

Figure 2*a,b* illustrates the profiles of clinical infections in the GP (solid curves) and HCWs (dashed curves), with an initial number of  $I(0)=100$  infectives. With clinical attack rates of 30 and 45% in the GP and HCWs, respectively, these figures demonstrate that not only can prophylaxis of HCWs contribute to a significant delay in the progression of the epidemic, but it can also substantially reduce the magnitude of the disease outbreak (figure 2*b*). While the outbreak appears in a greatly milder form with prophylaxis of HCWs, it can be affected by the initial size of the infected population. Simulations presented in figure 2*c,d* show that although the initial number of infectives has relatively low impact on the magnitude of the epidemic, it can dramatically influence the progression and peaking time of the outbreak.

An important public health concern is whether the combined effect of the treatment of clinical cases and the prophylaxis of HCWs can result in containing a pandemic. We performed an uncertainty analysis by considering a sampling approach that allows for the simultaneous variations of clinical attack rates ( $c_1$ ,  $c_2$ ) in the GP and HCWs, and the reduction in susceptibility to infection ( $\alpha_s$ ), as prophylaxis coverage increases. Using the Latin hypercube sampling (LHS) technique (McKay *et al.* 1979), we generated samples of size  $n=1000$ , in which each parameter is treated as a random variable and assigned a probability function. In this technique, the parameters are uniformly distributed and sampled within the ranges given in table 1.

The results of this uncertainty analysis are illustrated in box plots (figure 3) for the variations of the averaged control reproduction number ( $\mathcal{R}_a$ ). The quantity  $\mathcal{R}_a$  gives the average number of secondary infections generated by an infected individual (during the entire course of an outbreak) when control measures are implemented. In the presence of a treatment

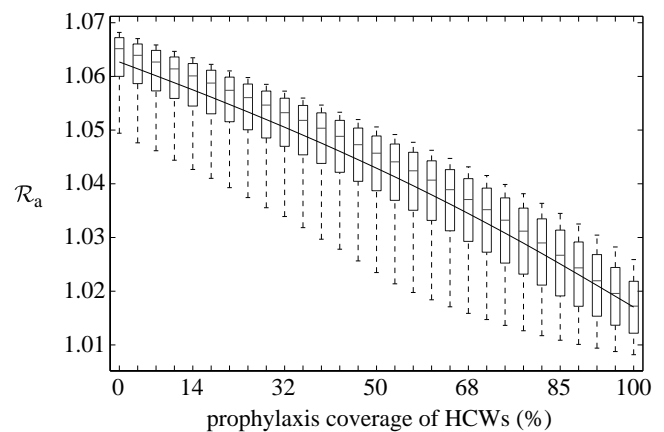


Figure 3. Sensitivity analysis: box plots for the variations of  $\mathcal{R}_a$  as prophylaxis coverage increases, with a curve passing through the mean values. Using 25% clinical attack rate in the GP, samples of size  $n=1000$  were generated by the LHS technique for the changes in susceptibility to the disease due to prophylaxis ( $\alpha_s$ : 25–35%) and a range of attack rate among HCWs ( $c_2$ : 25–40%).

strategy, we ran the simulations for different prophylaxis coverage of HCWs to evaluate the final size of the susceptible population  $S_\infty$ , when the epidemic dies out. We then used the final size relation (see electronic supplementary material) to calculate the corresponding values of  $\mathcal{R}_a$ . Figure 3 indicates that if an outbreak is expected to occur, prophylaxis of HCWs may not be able to prevent it. In this case, increasing prophylaxis coverage leads to a marginal reduction (4.3%) in the mean value of  $\mathcal{R}_a$  from 1.0627 (without prophylaxis) to 1.017 (with 100% prophylaxis coverage). An important epidemiological consequence is that prophylaxis of HCWs may not be considered as a disease control measure if the treatment of clinical infections fails to prevent the occurrence of an outbreak. We observed similar results when attack rates in the GP and HCWs vary between 25–35% and 25–50%, respectively. These observations demonstrate a reduction of less than 5% in the mean values of  $\mathcal{R}_a$  (table 3).

The effect of prophylaxis of HCWs may be deceptive, as its primary purpose is to maintain the quality of healthcare and reduce the disease burden, not to contain the epidemic. Our results shows that although the averaged control reproduction number is very marginally affected by expanding prophylactic treatment of HCWs, the potential substantial impact of this strategy appears to be limiting the spread of infection and reducing disease-related mortality. Box plots in figure 4*a* for the variations in the total number of recovered clinical infections show that the mean value is reduced by 72% (with full prophylaxis coverage of HCWs). A similar impact is observed in figure 4*b* with 73% reduction in the mean value of the total number of deaths in the population. The effectiveness of prophylaxis will be dramatically influenced by attack rates, and simulations reveal that the mean values of recovered clinical infections and deaths are reduced by 45 and 46%, respectively, when attack rates are increased by 30% in the GP and 30–45% among HCWs.

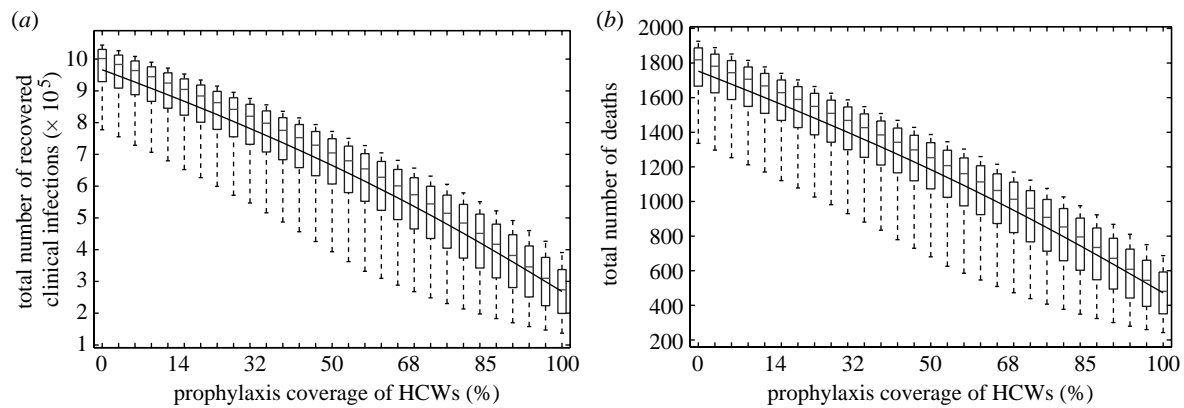


Figure 4. Sensitivity analysis: box plots for the variations of (a) the total number of recovered clinical infections and (b) the total number of deaths, as prophylaxis coverage increases. Using 25% clinical attack rate in the GP, samples of size  $n=1000$  were generated by the LHS technique for the changes in susceptibility to the disease due to prophylaxis ( $\alpha_S$ : 25–35%) and a range of attack rate among HCWs ( $c_2$ : 25–40%).

Table 3. Variations in the mean value of  $\mathcal{R}_a$  for different attack rates  $c_1$  and  $c_2$  in the GP and HCWs, as susceptibility to the disease due to prophylaxis changes ( $\alpha_S$ : 25–35%) and prophylaxis coverage of HCWs increases.

attack rate among HCWs (%)	variations in the mean value of $\mathcal{R}_a$			reduction (%)	attack rate in the GP (%)	$\mathcal{R}_0$
	prophylaxis coverage					
	0%	50%	100%			
25–40	1.0627	1.0445	1.0170	4.3	25	1.2516
30–45	1.0973	1.0795	1.0522	4.11	30	1.3261
35–50	1.1488	1.1326	1.1112	3.27	35	1.4146

## 5. DISCUSSION

The published literature suggesting that the use of neuraminidase inhibitors reduces susceptibility to influenza and substantially decreases the infectivity if infection occurs (Jefferson *et al.* 2006) has provided the basis for our study, assessing the effect of treatment and prophylaxis on reducing morbidity and mortality during a pandemic. The results show that maintaining high treatment level of clinical cases is essential for reducing fatality and containing a pandemic, regardless of the prophylaxis coverage of HCWs. In practice, however, the quality of healthcare system, and therefore the treatment level, is influenced by the number of HCWs who contribute to the caring for patients with influenza (Nguyen-Van-Tam *et al.* 1999; Simeonsson *et al.* 2004). Considering the nature of interaction between infected individuals and HCWs, the lack or poor administration of preventive measures may leave HCWs highly vulnerable to the infection, which in turn will compromise the effectiveness of the treatment strategy. For population demographics similar to those of Ontario, Canada, the findings suggest that with the full prophylaxis coverage of HCWs, a 45% reduction in population morbidity is achievable.

Given the available resources of public health, none of the previous studies (Meltzer *et al.* 1999; Balicer *et al.* 2005; Lee *et al.* 2006) addresses the fact that HCWs are central to any treatment or prophylaxis strategy. It should be emphasized that keeping HCW force in place

is critical not just to respond to the needed care of pandemic influenza patients, but also to prevent deaths from all other causes. Conventional wisdom considers access to inpatient and outpatient care to be central to any pandemic response. If modern healthcare resources were unavailable, ill individuals would not be able to access antivirals, antibiotics, oxygen therapy, intravenous therapy, intensive care and other therapies. The unavailability of these modern options during 1918–1919 undoubtedly contributed to the high mortality rate during that pandemic.

The WHO recommendations on non-pharmaceutical public health interventions call for the use of gowns, gloves and surgical masks to protect HCWs while providing care (WHO Writing Group 2006). While the use of such equipment may decrease the risk of transmission for an individual encounter with an infectious patient, the sheer number of encounters over the course of a working day would probably still result in disease transmission. Even with excellent infection control practices, attack rates of greater than 10% are likely to occur among HCWs in the absence of vaccination (Salgado *et al.* 2002). There is some evidence that infants, elderly and immunocompromised subjects may shed virus for several weeks (Salgado *et al.* 2002), which makes transmission of the disease even more difficult to control in the hospital and the community. It is also well recognized that even if protected at work, HCWs are just as probable as the GP to become infected outside of the workplace.

This study has several limitations that merit further discussion. Our model assumes homogeneous mixing, which may underestimate  $\mathcal{R}_0$  and result in a high sensitivity of the epidemic size to interventions, particularly at the early stages of an outbreak when stochastic effects play a dominant role in spreading the disease. Therefore, when the detailed structure of network contacts and mobility patterns are well identified, further evaluation of a prophylaxis strategy should provide more accurate quantitative predictions. We assumed that antiviral therapy will provide the same protection during a pandemic as it has been shown to provide in seasonal influenza. This assumption is common to other modelling studies (Longini *et al.* 2004, 2005; Ferguson *et al.* 2005). We have only considered the impact of prophylaxis of HCWs as it relates to the provision of antiviral treatment to the GP, yet we understand that HCWs provide far more care than this: hospital beds and modern therapies are essentially irrelevant without staffing. This simplification will result in an underestimation of the impact of prophylaxis of HCW on the morbidity and mortality of the GP. We have also considered all HCWs as a uniform group, yet they clearly fill different roles in the healthcare setting. Our model assumed that the supply of antiviral treatment for the entire course of the outbreak is secured. If the scarcity of antiviral drugs appears while the outbreak is peaking, it may leave HCWs susceptible to a high incidence of infection. This is unfavourable to the treatment strategy, which can be concomitant with a large absenteeism of HCWs due to the concern over infection at healthcare settings. This may suggest that susceptibility of HCWs at the early stages of an outbreak would become favourable to the treatment strategy by providing immunity upon recovery from the disease. However, a pandemic strain with high mortality rate, particularly in younger adults, can significantly affect the outcome of the treatment strategy. Finally, we have not considered the emergence of drug-resistant viral strains through the widespread or indiscriminate use of antiviral drugs (Moscona 2005; Rogers & Bonhoeffer 2006). This can substantially limit the impact of antiviral drugs and increase the likelihood of multiple pandemic waves caused by the evolution of resistant viral mutants.

Our findings suggest that the overall healthcare benefit of prophylaxis strategy may be much greater than other protective measures. The cost of providing universal oseltamivir prophylaxis to 135 025 HCWs in the province of Ontario is approximately \$CDN 316 000 per day or approximately 17.7 million dollars over an eight-week period. The necessary infrastructure to deliver this therapy would be an additional cost. While this strategy may appear cost prohibitive, its financial burden must be balanced with the inevitably far greater cost savings obtained through preventing substantial influenza-related morbidity and mortality in the GP. With the knowledge that prophylaxis of HCWs alone may not prevent the occurrence of an outbreak if expected, it may indeed be necessary to decelerate the spread of infection in the population and afford the time for vaccine manufacturing. While efforts are being made to shorten the delay in vaccine

availability, retarding the progression of the first pandemic wave is crucial for preventing excessive deaths and diminishing socio-economic disruption.

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