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Decision Making with Regard to Antiviral Intervention during an Influenza Pandemic

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Abstract

Background—Antiviral coverage is defined by the proportion of the population that takes antiviral prophylaxis or treatment. High coverage of an antiviral drug has epidemiological and evolutionary repercussions. Antivirals select for drug resistance within the population, and individuals may experience adverse effects. To determine optimal antiviral coverage in the context of an influenza outbreak, we compared 2 perspectives: 1) the individual level (the Nash perspective), and 2) the population level (utilitarian perspective).

Methods—We developed an epidemiological game-theoretic model of an influenza pandemic. The data sources were published literature and a national survey. The target population was the US population. The time horizon was 6 months. The perspective was individuals and the population overall. The interventions were antiviral prophylaxis and treatment. The outcome measures were the optimal coverage of antivirals in an influenza pandemic.

Results—At current antiviral pricing, the optimal Nash strategy is 0% coverage for prophylaxis and 30% coverage for treatment, whereas the optimal utilitarian strategy is 19% coverage for prophylaxis and 100% coverage for treatment. Subsidizing prophylaxis by \$440 and treatment by \$85 would bring the Nash and utilitarian strategies into alignment. For both prophylaxis and treatment, the optimal antiviral coverage decreases as pricing of antivirals increases. Our study does not incorporate the possibility of an effective vaccine and lacks probabilistic sensitivity analysis. Our survey also does not completely represent the US population. Because our model assumes a homogeneous population and homogeneous antiviral pricing, it does not incorporate heterogeneity of preference.

Conclusions—The optimal antiviral coverage from the population perspective and individual perspectives differs widely for both prophylaxis and treatment strategies. Optimal population and individual strategies for prophylaxis and treatment might be aligned through subsidization.

Keywords

mathematical models; economic evaluation; decision analysis

The pandemic potential of influenza, such as that of the currently circulating H1N1 swine influenza or that of the H5N1 avian influenza, is a major public health concern. The human

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population is immunologically susceptible to the antigenic novelties of H1N1, which resulted in a global pandemic as H1N1 virus evolved heightened transmissibility among humans.¹ Growing international experience in the treatment of pandemic H1N1 infections as well as the potential pandemic of H5N1 motivate considerable investment into preparedness strategies, but more research is needed to understand the adherence to preparedness strategies regarding antiviral drug use during a pandemic.

The antigenic characteristics of a pandemic influenza strain arising from cross-species transmission are virtually impossible to predict, making the availability of a vaccine during the first wave of a pandemic unlikely. Therefore, antiviral drugs that are broadly effective against influenza A subtypes and that can be stockpiled prior to zoonosis are fundamental to preparedness strategies,^{2–5} as antivirals can alleviate symptoms of influenza, enhance survival, and reduce transmissibility.⁶ In fact, due to the delayed development and distribution of H1N1 vaccines, antiviral drugs played a significant role as the first line of defense during the H1N1 influenza pandemic in 2009 to 2010.

Currently, 2 types of antiviral influenza drugs exist: M2 protein inhibitors (i.e., amantadine and rimantadine) and neuraminidase inhibitors (i.e., oseltamivir and zanamivir). The majority of avian influenza A viruses that have been transmitted to humans including H5N1 and H3N2 are now resistant to amantadine.⁷ Thus, for use during an influenza pandemic, the neuraminidase inhibitor oseltamivir is the antiviral drug of choice that has been recommended and stockpiled by the Centers for Disease Control and Prevention (CDC).⁸

Neuraminidase inhibitors such as oseltamivir and zanamivir block viral replication by preventing virions from being released from the surface of infected cells.⁹ For oseltamivir and zanamivir to fit into the neuraminidase active site, the amino acids must undergo a conformational change, and mutations that prevent this rearrangement may lead to resistance. For instance, the emergence of resistance to oseltamivir was reported in the US and China during the H1N1 pandemic.^{10,11} In addition, in H3N2 strains, de novo emergence of resistance occurs in 0.4% of outpatient adults and 5.5% of outpatient children treated with oseltamivir.¹² In contrast to oseltamivir, zanamivir is more structurally similar to the natural substrate of neuraminidase. Thus, resistance to zanamivir is less common.¹³ The stockpile of zanamivir has recently increased in response to resistance against oseltamivir, although at the current time, the stockpile is predominantly oseltamivir.^{14,15}

Antiviral prophylaxis and treatments have many benefits including reduced risk of severe illness or death. Prophylaxis lowers the risk of influenza, but that protection stops when the medication course is stopped. The recommended durations of treatment and prophylaxis are 5 days and 8 weeks, respectively. The impact of prophylaxis and treatment on the risk and severity of an infection not only depends on the prevalence of resistant strains but also on the willingness of individuals to adhere to public health recommendations. Such adherence is fundamental to determining the effectiveness of interventions. Therefore, mathematical predictions of individual decisions to adhere to prophylaxis and treatment are critical for the development of socially optimal interventions. Such predictions are also critical for our understanding of the risks of drug resistance. Application of game theory to these problems can be powerful tools to predict how the real or perceived dangers may hamper the willingness of individuals to adhere to public health recommendations.

From a game-theoretic perspective, an individual adopts a strategy that will minimize personal net cost. This net cost is increased by the probability of infection determined by disease prevalence, which is in turn governed by the prophylaxis and treatment decisions made by the rest of the population. An individual's decision is also subject to perceptions of

costs and benefits. These perceptions may deviate from epidemiological and economic reality and should be taken into consideration when parameterizing an epidemiological game-theoretic model of influenza transmission and antiviral interventions.

For individuals driven by self-interest, game-theoretic decisions are assumed to settle to a Nash equilibrium at which personal net cost cannot be decreased by making a different decision. We define these individual decisions of antiviral use at the Nash equilibrium as the Nash strategy. By contrast, the utilitarian strategy minimizes the overall net cost for the population as determined by the balance between the benefits and costs of antiviral interventions.¹⁶ The benefits of antiviral intervention are dependent on the prevalence of sensitive strains relative to that of resistant ones.

It has previously been found that the vaccination level for the Nash strategy is lower than for the utilitarian strategy due to the positive externality of herd immunity induced by vaccination.^{17–23} However, the potentially conflicting incentives of the individual and the population are more complicated in the case of antiviral intervention because both positive externalities and negative externalities can impact the population. From the perspective of the population, antivirals reduce the transmission of sensitive strains but also select for drug resistance. From the perspective of the individual, antiviral prophylaxis reduces the probability of infection, and antiviral treatment reduces the severity of infections at the risk of adverse effects. In addition to adverse effects and spread of resistance, the benefits of antiviral intervention are mitigated by costs and selection for drug resistance.^{6,24,25}

To predict the likely adherence to socially optimal interventions and examine the resulting impact of antivirals on influenza prevalence and on the evolution of drug resistance, we developed an epidemiological game-theoretic model of pandemic influenza that incorporates evolutionary dynamics of selection for drug resistance against oseltamivir. To parameterize our model, we conducted a national survey that examined how the public perceives the key epidemiological parameters for pandemic influenza, including infection risk, level of resistance, and efficacy and adverse effects of antivirals, as well as willingness-to-pay for antivirals during an influenza pandemic. We analyzed the intervention strategies of prophylaxis and treatment that would minimize net cost for the population overall and the likely adherence to these strategies at the level of the individual. For comparison, we also analyzed an epidemiological game-theoretic model of the intervention strategies using zanamivir.

METHODS

National Survey

We conducted a national Internet-based survey to examine how the public perceives the key epidemiological parameters for influenza pandemic and the benefits as well as the risks associated with antiviral drugs, including adverse effects and resistance evolution (Tables 1 and 2). Participants were recruited via a commercial survey firm. A total of 567 adults began the survey, and 502 completed the survey by providing all requested data. In the course of the survey, participants viewed two 2-minute slideshow tutorials on an influenza pandemic and on antivirals.^a The medication tutorial explained the difference between prophylaxis and treatment and the oseltamivir dosing for each, the concept of drug resistance, and the difference between drug-sensitive and drug-resistance infections. The survey included the items shown in Tables 1 and 2 about an influenza pandemic and about the use of antiviral medication to prevent and treat pandemic influenza. We compared predictions based on a

^aThese tutorials can be viewed at <http://www.rci.rutgers.edu/~mdmlab/avianflu/survey/flash/Avian.swf> and <http://www.rci.rutgers.edu/~mdmlab/avianflu/survey/flash/Antiviral.swf>.

perceived parameter set with predictions based on a normative parameter set (Tables 1 and 3). Because the distribution for some items is skewed, we chose to use the median values of response rather than the mean. Based on median values of response to each survey item, we calculated their perceived cost of disease and adverse effects of antiviral medication.

Epidemic Model

We developed a compartmental model of an influenza pandemic and an oseltamivir-based control strategy (Fig. 1). We also present the model that combines our prophylaxis and treatment models because, in reality, both prophylaxis and treatment are likely to be used in the population simultaneously (Appendix). Sensitivity analysis was performed by varying key parameters such as drug costs and efficacy of antiviral drugs.

Epidemiological Population Model

We developed a compartmental model for influenza transmission that incorporates the use of antivirals. We assumed that all individuals are initially immunologically susceptible to the novel influenza strain. The prevalence of infection by sensitive and resistant strains was calculated based on final epidemic size from our epidemic model. These prevalences of infection were then used to calculate probability of infection by sensitive and resistant strains. Then, the probability of infection was used to parameterize the expected cost of disease and antivirals (Tables 3 and 4). We used Monte Carlo methods parameterized with the calculated net costs in order to determine Nash equilibria and utilitarian strategies. In the absence of antivirals, resistant strains are less transmissible than drug-sensitive strains.^{6,25–27} Lipsitch and others assumed a 10% reduction in transmissibility accounting for the reduction in the fitness of resistant strains,²⁵ and Perelson and others assumed a 0% to 20% reduction relative to drug-sensitive strains.⁶ As a baseline parameter, we assumed that susceptible individuals become infected at a rate proportional to the number of infected individuals and that resistant strains are 10% less transmissible than drug-sensitive strains (Table 3).^{6,25–27} We define β_{SU} as the transmissibility of the wild-type strain without antiviral treatment and β_R as the transmissibility of the resistant strain ($\beta_R = 0.9\beta_{SU}$).

Prophylaxis—Our prophylaxis model (equations 1–5) consists of 5 epidemiological classes: susceptible (S), prophylaxed (S_p), infected with a sensitive strain (I_{SU}), infected with a resistant strain (I_R), and recovered from influenza (R) (Fig. 1A). Prophylaxed individuals become infected at a fraction $(1 - e_p)$ of the rate at which nonprophylaxed susceptible individuals become infected, where e_p is the efficacy of prophylaxis in reducing susceptibility to the drug-sensitive strain (0.85 as the baseline value). We also assumed that prophylaxis causes de novo resistance (r_p) at a probability of 0.02% and that the mean duration of infectiousness is 4 days ($1/\gamma$) (Table 3). We further assumed that drug-resistant strains at the beginning of a pandemic comprise 4% of all strains, as indicated by epidemiological studies,^{28–30} and denoted the proportion of the population that takes antiviral prophylaxis as coverage (ϕ). We define α as disease-related mortality. Given these assumptions, the prophylaxis model can be expressed by the following deterministic system of ordinary differential equations:

$$S' = -(\beta_{SU}I_{SU} + \beta_R I_R) S / N, \quad (1)$$

$$S'_p = -[(1 - e_p)\beta_{SU}I_{SU} + \beta_R I_R] S_p / N, \quad (2)$$

$$I'_{SU} = \beta_{SU}I_{SU} S / N + (1 - e_p - r_p)\beta_{SU}I_{SU} S_p / N - (\gamma + \alpha)I_{SU}, \quad (3)$$

$$I'_R = \beta_R I_R (S + S_P) / N + r_p \beta_{SU} I_{SU} S_P / N - (\gamma + \alpha) I_R, \quad (4)$$

$$R' = \gamma (I_{SU} + I_R), \quad (5)$$

where $S(0) = (1 - \phi)\{N(0) - 1\}$, $S_P(0) = \phi N(0)$, $I_{SU}(0) = 0.96$, $I_R(0) = 0.04$, $R(0) = 0$, and $N = S + S_P + I_{SU} + I_R + R$.

The basic reproduction ratio is the number of drug-sensitive/drug-resistant infections in a totally susceptible population caused by a single drug-sensitive/drug-resistant infection over infectious periods in the absence of interventions to control the infection.³¹ The effective reproduction ratio is similarly defined in the presence of control measures to limit disease transmission. Mathematically, the effective reproductive ratio is given by the largest eigenvalue of the (nonnegative) matrix $\mathbf{M}$, where $\mathbf{M}$ is given by

$$\mathbf{M} = \frac{1}{\gamma + \alpha} \begin{pmatrix} \beta_{SU}\{1 - (e_p + r_p)\phi\} & 0 \\ r_p \beta_{SU} \phi & \beta_R \end{pmatrix}.$$

The element $m_{11} = \frac{\beta_{SU}\{1 - \phi(e_p + r_p)\}}{\gamma + \alpha}$ represents the number of secondary infections when a single drug-sensitive infection is introduced and a proportion, ϕ , of the population is on

prophylaxis. Similarly, $m_{22} = \frac{\beta_R}{\gamma + \alpha}$ represents the number of secondary infections by a single

drug-resistant infection in a totally susceptible population. The element $m_{21} = \frac{r_p \beta_{SU} \phi}{\gamma + \alpha}$ represents the average number of infections caused by de novo resistance due to prophylaxis. Thus, the effective reproductive ratio is given by

$$R_c = \max \left\{ \frac{\beta_{SU}\{1 - \phi(e_p + r_p)\}}{\gamma + \alpha}, \frac{\beta_R}{\gamma + \alpha} \right\}. \text{ In the absence of the use of prophylaxis, the basic}$$

reproductive ratio is defined by $R_0 = \max \left\{ \frac{\beta_{SU}}{\gamma + \alpha}, \frac{\beta_R}{\gamma + \alpha} \right\} = \frac{\beta_{SU}}{\gamma + \alpha}$ because $\beta_{SU} > \beta_R$. Here, the basic reproductive number for a sensitive strain in the absence of a control measure is assumed to be 1.2, which amounts to a 32% attack rate (i.e., a final proportion of the population infected) during an influenza pandemic.^{32–35}

Treatment—Our treatment model (equations 6–10) replaces the prophylaxed class (S_P) from the prophylaxis model (equations 1–5) with a treated class (I_{ST}). We define f_T as the probability at which an infected individual chooses to use antivirals to treat his or her infection (Fig. 1B). For drug-sensitive infections, antiviral drug treatment decreases viral loads^{36,37} and thus is assumed to reduce the transmissibility to β_{ST} , which is 66% lower than β_{SU} , and the infectious period to $1/\gamma_T$, which is 25% shorter than $1/\gamma$ (Table 3).^{25,38} We also define r_T as a fraction of treated individuals infected with drug-sensitive strains who acquire de novo resistance (0.2% as baseline value) (Table 3).²⁵ Therefore, the model for antiviral treatment is given by the following:

$$S' = -(\beta_{ST} I_{ST} + \beta_{SU} I_{SU} + \beta_R I_R) S / N, \quad (6)$$

$$I'_{ST} = f_T (1 - r_T) (\beta_{ST} I_{ST} + \beta_{SU} I_{SU}) S / N - (\gamma_T + \alpha_T) I_{ST}, \quad (7)$$

$$I'_{SU} = (1 - f_T)(\beta_{ST}I_{ST} + \beta_{SU}I_{SU})S/N - (\gamma + \alpha)I_{SU}, \quad (8)$$

$$I'_R = f_T r_T (\beta_{ST}I_{ST} + \beta_{SU}I_{SU})S/N + \beta_R I_R S/N - (\gamma - \alpha)I_R, \quad (9)$$

$$R' = \gamma I_{ST} + \gamma I_{SU} + \gamma I_R, \quad (10)$$

where $S(0) = N(0) - 1$, $I_{ST}(0) = 0$, $I_{SU}(0) = 0.96$, $I_R(0) = 0.04$, and $R(0) = 0$.

The effective reproductive ratio is $R_c = \max \left\{ \frac{f_T(1 - r_T)\beta_{ST}}{\gamma_T + \alpha_T} + \frac{(1 - f_T)\beta_{SU}}{\gamma + \alpha}, \frac{\beta_R}{\gamma + \alpha} \right\}$. The basic reproductive ratio is defined by $R_0 = \max \left\{ \frac{\beta_{SU}}{\gamma + \alpha}, \frac{\beta_R}{\gamma + \alpha} \right\} = \frac{\beta_{SU}}{\gamma + \alpha}$ because $\beta_{SU} > \beta_R$.

Calculations of Net Cost

To calculate the average individual net cost of disease associated with an intervention strategy, we incorporated the costs associated with infection, antivirals, and possible adverse effects. The cost of infection includes the probability and severity of possible infection outcomes such as work loss, outpatient visits, medication, hospitalization, and mortality (Table 4). We denoted the parameter sets derived from the survey and epidemiologically verified data as perceived and normative parameters, respectively. For the calculation of Nash strategy based on perceived parameters, we used the survey results of questions related to willingness-to-pay (Table 2). The cost of antiviral treatment was prorated at 19% ($\approx \$85/\454) of the cost of prophylaxis based on its higher dosages but shorter duration (Table 4). The perceived cost for adverse effects was calculated from the difference of survey responses about the public's willingness-to-pay for antivirals with and without possible adverse effects (Table 2). To calculate the normative cost of these effects, we employed the conversion that a quality-adjusted life-year (QALY) is monetarily equivalent to \$50,000.³⁹⁻⁴¹ The cost of mortality was valued at \$1,045,278 using average expected future lifetime earnings.^{33,42} For sensitivity analysis, lower costs of mortality, that is, 50% and 75% of \$1,045,278, were used.

The net cost of antiviral refusal is defined as the expected individual cost of infection for those who do not receive antivirals during a pandemic. Conversely, the net cost of antiviral acceptance is calculated as the expected cost of infection for those who receive antivirals. For instance, if an individual infected with a sensitive strain is treated with antivirals, the infection severity is usually reduced. Thus, we incorporated the reduction in the costs for individuals with antiviral treatment (Table 4). The utilitarian strategy is defined as the level of antiviral coverage at which the average individual cost is minimized. The average individual cost is the sum of the net costs of antiviral acceptance and antiviral refusal weighted according to the likelihood of seeking antivirals.

Calculation of Nash and Utilitarian Strategies

If the rest of the population adopts a control strategy of antiviral use at probability, P ($P = \phi$ for prophylaxis, and $P = f_T$ for treatment), and the net cost to an individual of desiring antivirals is the same as refusing a control strategy, then P is defined as a Nash strategy. Thus, at the Nash strategy, the net cost of disease when antivirals are used is equal to the net cost of disease when antivirals are refused.⁴³ The calculations of Nash equilibria are achieved through single parameter optimization. That is, we searched for a probability of

antiviral use (ϕ for prophylaxis, and f_T for treatment) that minimizes the difference between expected costs of antiviral acceptance and refusal.

For our prophylaxis model, the expected costs of antiviral acceptance ($Q_{1,p}$) and refusal ($Q_{2,p}$) are

$$Q_{1,p} = \frac{\int_{t=0}^{t_f} \{(1 - e_p) \beta_{SU} I_{SU} + \beta_R I_R\} S_p / N dt}{S_p(0)} \cdot C_1 + C_{3,p} + p(REV_p) \cdot C_{4,p}$$

and

$$Q_{2,p} = \frac{\int_{t=0}^{t_f} (\beta_{SU} I_{SU} + \beta_R I_R) S / N dt}{S(0)} \cdot C_1,$$

respectively (see Table 3 for descriptions of variables). Here,

$\int_{t=0}^{t_f} \{(1 - e_p) \beta_{SU} I_{SU} + \beta_R I_R\} S_p / N dt$ describes the cumulative number of infections by drug-sensitive or -resistant strains among individuals who are on prophylaxis, and $S_p(0)$ is the number of total individuals who are on prophylaxis. Also, $S(0)$ is the number of total individuals who refuse prophylaxis, and we denote the duration of an influenza pandemic as t_f . Thus, the first term in $Q_{1,p}$ is the cost of infection multiplied by the probability of infection by drug-sensitive or -resistant strains among persons who are on prophylaxis. The cost of disease among individuals who accept prophylaxis ($Q_{1,p}$) also includes the cost of antivirals ($C_{3,p}$) and that of possible adverse effects ($p(REV_p) \cdot C_{4,p}$). Similarly, the first term in $Q_{2,p}$ is the cost of infection multiplied by the probability of infection by drug-sensitive or -resistant strains among persons who are not on prophylaxis. Here,

$\int_{t=0}^{t_f} (\beta_{SU} I_{SU} + \beta_R I_R) S / N dt$ describes the cumulative number of infections by drug-sensitive or -resistant strains among individuals who refuse prophylaxis.

For our treatment model, the expected costs of antiviral acceptance ($Q_{1,T}$) and refusal ($Q_{2,T}$) are $Q_{1,T} = P(R) \cdot C_1 + P(S) \cdot C_2 + C_{3,T} + p(REV_T) \cdot C_{4,T}$ and $Q_{2,T} = C_1$, respectively, where $P(S)$ is the probability that infection is caused by drug-sensitive strains, and $P(R)$ is the probability that infection is caused by drug-resistant strains. If infection is caused by drug-sensitive strains, treatment would reduce the severity of symptoms. Therefore, the cost of infections would be lower with treatment than without, that is, $C_1 > C_2$. However, if infection is caused by drug-resistant strains, treatment would not reduce the severity of symptoms, so the cost of infections (C_1) would not be different whether individuals seek

$$P(S) = \frac{\int_{t=0}^{t_f} (1 - f_T r_T) (\beta_{ST} I_{ST} + \beta_{SU} I_{SU}) S / N dt}{\int_{t=0}^{t_f} (\beta_{ST} I_{ST} + \beta_{SU} I_{SU} + \beta_R I_R) S / N dt}$$

treatment or not. Thus, we define $P(S)$ and $P(R)$ as

and $P(R) = 1 - P(S)$ (Table 3). Here, $\int_{t=0}^{t_f} (1 - f_T r_T) (\beta_{ST} I_{ST} + \beta_{SU} I_{SU}) S / N dt$ describes the cumulative incidence of drug-sensitive strains including successfully treated

$\left(\int_{t=0}^{t_f} f_T (1 - r_T) (\beta_{ST} I_{ST} + \beta_{SU} I_{SU}) S / N dt \right)$ and untreated cases $\left(\int_{t=0}^{t_f} (1 - f_T) (\beta_{ST} I_{ST} + \beta_{SU} I_{SU}) S / N dt \right)$,
 while $\int_{t=0}^{t_f} (\beta_{ST} I_{ST} + \beta_{SU} I_{SU} + \beta_R I_R) S / N dt$ describes the cumulative incidence of both drug-sensitive and drug-resistant strains.

The utilitarian optimum was calculated by minimizing the expected cost of the population. That is, we search for $\phi \in [0, 1]$ that minimizes $[(1 - \phi) \cdot Q_{1,P} + \phi \cdot Q_{2,P}]$ for prophylaxis

and $f_T \in [0, 1]$ that minimizes $[(1 - f_T) \cdot Q_{1,T} + f_T \cdot Q_{2,T}] \frac{\int_{t=0}^{t_f} (\beta_{ST} I_{ST} + \beta_{SU} I_{SU} + \beta_R I_R) S / N dt}{N(0)}$ for treatment.

For the treatment model, the epidemic size, $\left(\frac{\int_{t=0}^{t_f} (\beta_{ST} I_{ST} + \beta_{SU} I_{SU} + \beta_R I_R) S / N dt}{N(0)} \right)$, is incorporated because only infected individuals can decide to seek antiviral treatment, whereas decisions regarding prophylaxis can be made early on, before an epidemic. For the calculation of the utilitarian optimum of antiviral treatment strategies, the epidemic size is incorporated into the calculation of disease cost because antiviral treatment is only applicable to those who are infected, whereas everyone is assumed to make decisions on prophylaxis at the beginning of the outbreak. To determine the likely impact of improved education about influenza and its antiviral drugs, we compared the Nash strategy based on normative epidemiological parameter values with the Nash strategy based on perceived parameter values obtained from our survey data. In contrast, the utilitarian strategies are always based on normative parameters hereafter. We also evaluated the impact of subsidies and misconceptions about the risk of antivirals by varying the cost of antivirals and influenza-related parameters. Furthermore, we determined the sensitivity of our results to variation in antiviral efficacy.

RESULTS

Survey

The age distribution of the surveyed group was comparable to the adult US population, with a mean age of 46.5 years (range, 18–89). The sample was 80% female and 80% white. The median income was in the \$40,000 to \$50,000 range, 38% of participants had a college degree, 51% were married, and 57% were employed full or part time. Our survey indicates that perceptions of the transmissibility and the prevalence of pandemic influenza infection are overestimated (Table 1). All but one of the median responses were statistically significantly different from the corresponding normative values. Individuals overestimated the probability of infection by the resistant strain but tended to underestimate the efficacy of antivirals. Our survey also indicates that individuals were willing to pay statistically significantly more for a prophylactic measure that “works like magic” without adverse effects than for the actual medication ($P < 0.0001$) (Table 2).

Epidemiological Consequences of Antiviral Interventions

We assessed the epidemiological consequences of administering antivirals at various coverage levels as either prophylaxis or treatment using normative parameters (equations 1–10). Generally, probability of infection by drug-sensitive strains decreases for the entire population as the proportion of the population who receive prophylaxis increases (Fig. 2A).

However, as more individuals accept prophylaxis during a pandemic, the spread of resistance accelerates. Therefore, as prophylaxis increases, the probability of infection among prophylaxed individuals ceases to decrease once a resistant strain becomes prevalent (Fig. 2A).

Our calculations also indicate that antivirals have the potential to suppress the proportion of the population infected to about 3% of the population if the prophylaxis or treatment in the population is sufficient (Figs. 2A and 2C). We found that the further transmission by a sensitive strain can be reduced to a negligible level at 60% (or higher) coverage of prophylaxis or at 80% (or higher) coverage of antiviral treatment. When the risk of infections by the sensitive strain is negligible, individuals who are not prophylaxed share the same probability of infection as prophylaxed individuals. Thus, the net cost of disease associated with an individual's decision to receive prophylaxis depends on the overall prophylaxis coverage in the population.

Nash and Utilitarian Strategies

At current antiviral pricing (\$454/8 weeks), the Nash strategy with perceived or normative parameters for prophylaxis is for individuals to refuse antivirals. This refusal would result in 315,400 infections and 151 deaths per million individuals (Figs. 2 and 3). In contrast, the utilitarian strategy would be to distribute antiviral drugs to 19% of the population (Fig. 3). This strategy would lead to 43,300 infections and 21 influenza-related deaths per million individuals, which is 272,100 fewer infections than predicted from the Nash strategy (Figs. 2 and 3). Thus, at current drug prices, prophylaxis would result in a lower probability of infection if the utilitarian strategy is followed (0.04%) than if the Nash strategy is followed (31.5%). Nevertheless, for the prophylaxis model, the subsidy of \$440 would bring the Nash strategy into alignment with the utilitarian strategy when the Nash strategy is calculated based on perceived parameters.

In contrast, our simulations show that when antivirals are used as treatment, the utilitarian and Nash strategies based on normative parameters are 100% coverage at the current price of antivirals (\$85/5 days). Such 100% acceptance would result in 24,800 infections and 12 influenza-related deaths per million individuals (Figs. 2 and 3). For the Nash strategy of antiviral treatment based on perceived parameters, on the other hand, 30% coverage is predicted (Fig. 3B), resulting in 34,300 infections and 15 influenza-related deaths per million individuals (Figs. 2 and 3). Furthermore, the coverage at the Nash strategy based on perceived parameters falls rapidly as costs increase, indicating that individual demand is more sensitive to the change in antiviral pricing than the utilitarian optimum is (Fig. 3B). Nevertheless, at the current antiviral pricing, subsidization of \$85 would be able to align the Nash and utilitarian strategies if individuals made decisions based on their beliefs.

Our analyses also indicate that the discordance between the coverage of antivirals at the Nash strategy and that at the utilitarian strategy is higher for prophylaxis than for treatment, although it decreases with rising costs of antivirals (Figs. 3A and 3B). Both the Nash and utilitarian strategies are higher for antiviral treatment than for prophylaxis because treatment has immediate benefits that are directly targeted to infected individuals.

In addition to carrying out the analyses that consider the use of oseltamivir, we also assessed the use of zanamivir for which the level of resistance is negligible (Figs. A1 and A2).⁴⁴ We determined that the Nash and utilitarian strategies based on normative parameters for zanamivir are higher than those for oseltamivir because resistance does not emerge with zanamivir and the risk of adverse effects is low, that is, 5%. For instance, the prophylaxis acceptance (33%) at the utilitarian strategy substantially increases for zanamivir, indicating that the emergence of resistance detracts the effectiveness of oseltamivir.

Sensitivity Analysis

For sensitivity analysis, we studied how the utilitarian and the Nash strategies based on normative parameters change as the cost of mortality is lowered (Figs. 4 and 5). We found that, as the cost of mortality becomes lower, the antiviral acceptance at the utilitarian and the Nash strategies tends to decrease. At the current antiviral pricing, the utilitarian strategies for prophylaxis are 17% and 18% acceptance when the costs of mortality are \$52,139 and \$783,959, respectively, whereas the Nash strategy of prophylaxis is 0% acceptance for both costs of mortality (Fig. 4). Nevertheless, such decreases in antiviral acceptance were more pronounced for prophylaxis than for treatment. In fact, at the current antiviral pricing, it is found that both the utilitarian and the Nash treatment strategies are 100% acceptance whether the cost of mortality is \$52,139 or \$783,959. Therefore, the amount of subsidy required to bring the Nash treatment strategy into alignment with the utilitarian strategy does not change, even if we use lower cost of mortality in calculation of the cost of antiviral refusal and acceptance (Fig. 5).

We also conducted sensitivity analyses of the Nash strategy for perceived parameters and for the utilitarian strategy for normative parameters by varying key parameters, drug costs and efficacy (Figs. 6 and 7). We found that for most drug costs, the prophylaxis coverage at the utilitarian optimum is more sensitive to change in drug efficacy than that at the Nash strategy. For drug costs higher than \$100, the Nash strategy based on perceived parameters is to reject antiviral prophylaxis even if drug efficacy is sufficiently high. In contrast, the utilitarian optimum of prophylaxis initially increases but decreases eventually as drug efficacy increases. This is because the reduction in the prevalence of sensitive strains increases as drug efficacy becomes higher; however, the selection for resistance becomes stronger simultaneously.

Sensitivity analyses of the Nash treatment strategy for perceived parameters and utilitarian treatment strategies for normative parameters are shown in Figure 7. We found that both the coverage at the Nash strategy and utilitarian optimum increases as the efficacy of antivirals in reducing transmissibility increases. However, the Nash strategy for antiviral treatment is more elastic to the drug costs than drug efficacy. These findings highlight the potential increase in the coverage of antiviral treatment when subsidy is provided.

Nash and Utilitarian Strategies When Prophylaxis and Treatment Are Simultaneously Used

When we consider prophylaxis and treatment simultaneously with the coverage of treatment fixed at 30%, the utilitarian strategy as well as the Nash strategy based on normative or perceived parameters are to reject prophylaxis (Figs. A3 and A4). In contrast, when we consider prophylaxis and treatment simultaneously with the coverage of prophylaxis fixed at 10%, the Nash and utilitarian strategies based on normative parameters are 100%, whereas the Nash strategy based on perceived parameters is 18% (Fig. A5), indicating that the misperceptions on antivirals and influenza pandemics might lower the demand for antiviral drugs. If the coverage of prophylaxis is fixed at 10%, subsidization of \$45 would be able to align the Nash and utilitarian strategies, that is, 100% acceptance of antiviral treatment.

DISCUSSION

We evaluated optimal coverage of antiviral drug use for both the individual and the population during an influenza pandemic. Our results show that the demand for antiviral drugs driven by self-interest during such a pandemic would likely be far lower than that which would minimize overall net cost for the population. This is because the beneficial and detrimental outcomes of antiviral use generate conflicts between the Nash strategy for an individual and the utilitarian strategy optimal for the population overall. The source of these

discrepancies, for both antiviral treatment and prophylaxis, is a combination of positive externalities associated with reduced transmission in the population and the negative externalities of selection for drug resistance.

Our analyses show that the discrepancy between the Nash strategy and the utilitarian strategy is larger when antivirals are used for treatment than when they are used for prophylaxis, if individual decisions are made based on their own beliefs. The conflict between the individual and the population (or public health officer) is most pronounced as the cost of antiviral drug treatment increases. In fact, at the cost of antiviral treatment as high as \$400, it is expected that public health still favors 100% acceptance of antiviral treatment and aims at minimizing the prevalence of drug-sensitive strains, whereas individuals are likely to reject antivirals. Increasing antiviral costs has a greater impact on individuals than on the population because the positive externality of reduced transmission comes into play for the latter.

To bring the Nash and utilitarian strategies into alignment for antiviral treatment at current antiviral pricing, \$85 of subsidization would be required. Such subsidization can be greatly reduced, however, if there are also public health campaigns to educate about pandemic influenza. For antiviral prophylaxis, the Nash strategy is to reject antivirals at current drug pricing. If individual decisions are made with misperception, subsidization of \$440 would be required to align the Nash and utilitarian strategies. Thus, from the population perspective, more subsidies are necessary to promote prophylaxis than antiviral treatment.

Overall, complete prevention or near eradication of drug-sensitive strains is rarely possible without subsidy or education about antivirals, if individuals have the incentive to take less antiviral drugs than is optimal from the population perspective. When prophylaxis and treatment are applied simultaneously, the antiviral acceptance at the Nash and utilitarian strategies for treatment with prophylaxis is lower than that for treatment without prophylaxis. This is because the prevalence of circulating resistant strains is reduced when both prophylaxis and treatment are in use. Based on these findings, the benefit of antivirals can be strengthened when a low level of prophylaxis is used in the population in combination with treatment.

To simplify our model and its analysis, our calculations had several limitations. We assumed that the details of population structure and heterogeneity of antiviral drug use play a minor role in the perceived and normative data collected. We also did not carry out probabilistic sensitivity analysis, which would have allowed us to explore the uncertainty of our model. Moreover, we have not taken such combination therapy of oseltamivir and zanamivir into account here, but the drugs' synergistic effect in suppressing the emergence of antiviral resistance may be worth looking into. Indeed, circulating oseltamivir-resistant strains are known to be sensitive to zanamivir; thus, combination therapy may dampen the spread of resistant strains.

Our study revealed important discrepancies between the utilitarian and the Nash strategies of antivirals in the event of an influenza pandemic. By establishing public health policies that provide subsidies, externalities arising from the use of antivirals can be internalized into the Nash strategy to promote antiviral coverage that is optimal for the population. Also, public health policies that promote education about influenza and its antiviral drugs may be critical to promote public adherence and to minimize morbidity and mortality in the population overall. In addition, the Nash strategies calculated based on perceived parameters at various pricing can also be interpreted as the demand for antiviral drugs. Such prediction can provide invaluable insights when a preparedness plan for an influenza pandemic is based on the limited stockpile of antiviral drugs. Our findings not only assessed how the public and

individual interests are shaped by public misperception about influenza, antivirals, and the cost of antiviral drugs, it also can be used to aid in guiding the decisions of individuals and public health officers when faced with an influenza pandemic.

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Figure 1.

(A) Flow diagram of prophylaxis model. (B) Flow diagram of treatment model.

Figure 2.

Optimal antiviral strategies for the influenza pandemic using normative and perceived parameter values and the effects of antiviral use on final epidemic size as coverage in the population varies. (Baseline normative parameters: $\beta_{SU}=0.30$, $\beta_{ST}=0.20$, and $\beta_R=0.27$. Baseline perceived parameters: $\beta_{SU}=0.09$, $\beta_{ST}=0.050$, and $\beta_R=0.079$. See Table 3 for other parameters.) (A) Final epidemic size for the prophylaxis strategy. The strain-specific (drug-sensitive and drug-resistant) epidemic sizes as well as total epidemic size are shown as coverage in the population varies. (B) Final epidemic size for the treatment strategy. The strain-specific (drug-sensitive and drug-resistant) epidemic sizes as well as total epidemic size are shown as coverage in the population varies.

Figure 3.

(A) Individual and population optima for prophylaxis. Blue dashed: utilitarian strategy; red: Nash strategy based on normative parameters; black dotted: Nash strategy based on perceived parameters. (Baseline normative parameters: $\beta_{SU}=0.30$, $\beta_{ST}=0.20$, and $\beta_R=0.27$. Baseline perceived parameters: $\beta_{SU}=0.099$, $\beta_{ST}=0.050$, and $\beta_R=0.079$. See Table 3 for other parameters.) (B) Individual and population optima for treatment. (C) Mortality per 1,000,000 individuals when the coverages of antiviral prophylaxis are at the Nash and utilitarian strategies. (D) Mortality per 1,000,000 individuals when the coverages of antiviral treatment are at the Nash and utilitarian strategies.

Figure 4.

Optimal prophylaxis strategies for the influenza pandemic using normative and perceived parameter values as well as various costs of mortality. Blue dashed: utilitarian strategy; red: Nash strategy based on normative parameters; black dotted: Nash strategy based on perceived parameters. (A) Individual and population optima for prophylaxis when \$783,958 (75% of \$1,045,278, the baseline value of the cost of mortality) is used as the cost of mortality. (B) Individual and population optima for prophylaxis when \$522,639 (50% of \$1,045,278) is used as the cost of mortality.

Figure 5.

Optimal treatment strategies for the influenza pandemic using normative and perceived parameter values as well as various putative willingness-to-pay thresholds. Blue dashed: utilitarian strategy; red: Nash strategy based on normative parameters; black dotted: Nash strategy based on perceived parameters. (A) Individual and population optima for treatment when \$783,958 (75% of \$1,045,278, the baseline value of the cost of mortality) is used as the cost of mortality. (B) Individual and population optima for treatment when \$522,639 (50% of \$1,045,278) is used as the cost of mortality.

Figure 6. Nash (A) and utilitarian (B) strategies of prophylaxis for various antiviral costs and efficacies.

Figure 7.
Nash (A) and utilitarian (B) strategies of treatment for various antiviral costs and efficacies.

Table 1
Mean Responses to Selected Survey Items and Epidemiological Baseline Parameter Values

Questionnaire Item	Median	Interquartile Range	Mean	Standard Deviation	Epidemiological Value	P	Symbol
During a pandemic, some people are infected with “drug-sensitive” virus strains, and other people are infected with “drug-resistant” virus strains. Suppose there is an Avian flu pandemic in your community of 100,000 people. Of the small number of people who are infected at the very start of the pandemic, 96% are infected with drug-sensitive strains of the flu virus, and 4% are infected with drug-resistant strains. Imagine that neither the Avian flu vaccine nor antiviral medicines are available, so no one can get vaccinated or take antiviral medications. Eventually the pandemic will end: there will be no new infections, and everyone who has been infected will either recover or die. By the end of pandemic, how many people out of the 100,000 people in your community have been infected with Avian flu at some point during the pandemic?	50,000	86,000 (4000–90,000)	49,762	40,699	77,000 ^{45–47}	<0.0001	Translated to β_{ST}
100, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10,000, 11,000, 12,000, 13,000, 14,000, 15,000, 16,000, 18,000, 20,000, 25,000, 30,000, 35,000, 40,000, 45,000, 50,000, 60,000, 70,000, 80,000, 90,000, 100,000							
During an Avian flu pandemic, the drug-resistant virus strains are spread less easily from person to person than are the drug-sensitive virus strains. How transmissible do you think the drug-resistant virus strains are compared to the drug-sensitive ones?	80%	100% (0%–100%)	66%	58%	90% ²⁵	<0.0001	Translated to β_R
The drug-resistant strains are ____% as transmissible as the drug-sensitive strains. 0%, 20%, 40%, 60%, 80%, 100%, 120%, 140%, 160%, 180%, 200%							
How effective do you think the antiviral medication is in preventing you from transmitting the influenza virus from you to other people? 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%	50%	40% (30%–70%)	51%	28%	66% ³⁸	<0.0001	Translated to β_{ST}
How effective do you think the antiviral medication is in preventing death? 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%	60%	30% (50%–80%)	61%	26%	63% ^{33,48–50}	<0.0001	Translated to benefits of antivirals
Suppose you were infected with Avian flu and you <i>have not</i> received antiviral medication. How many days do you think you would stay infected? ____ days 0, 1, 2, 3, 4, 5, 6, 7, 10, 14, 21, 30, 60, 90	14 days	50 (10–60)	32.27	30.65	4 days ^{51,52}	<0.0001	1/ γ
Suppose you were infected with Avian flu. You are a person who would respond to antiviral medication, and you <i>have</i> received antiviral medication. How many days do you think you would stay infected? ____ days 0, 1, 2, 3, 4, 5, 6, 7, 10, 14, 21, 30, 60, 90	10 days	9 (5–14)	16.21	20.65	3 days ^{53,54}	<0.0001	Translated to R_C
How effective do you think prophylactic antiviral medication is at preventing you from getting infected with Avian flu? 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%	60%	30% (50%–80%)	60%	26%	85% ³⁸	<0.0001	e_P

Questionnaire Item	Median	Interquartile Range	Mean	Standard Deviation	Epidemiological Value	P	Symbol
Imagine that you are taking prophylactic antiviral medication. How likely is it that, as a result of taking this medication, you will become resistant to the medication? ___ in 10,000 chance	10%	48% (2%–50%)	25.83%	28.31%	0.02% ²⁵	<0.0001	r_P
0, 2, 20, 100, 200, 300, 400, 500, 1000, 2000, 3000, 4000, 5000, 7000, 10,000							
Imagine that you are infected with Avian flu and taking antiviral medication to treat the infection. How likely is it that, as a result of taking this medication, you will become resistant to the medication? ___ in 10,000 chance	10%	48% (2%–50%)	23.34%	26.07%	0.2% ²⁵	<0.0001	r_T
0, 2, 20, 100, 200, 300, 400, 500, 1000, 2000, 3000, 4000, 5000, 7000, 10,000							
Imagine that you have not been infected with Avian flu, but there is a chance you could become infected. You could take antiviral medication as a precaution. How likely would you be to take antiviral medication as a prophylactic (protective) measure if it were available to you for \$455 for the duration of the flu season?	40%	80% (0%–80%)	43%	37%	Varied		Translated to $S_P(0)$
0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%							
Imagine that you were infected with Avian flu and you know you are infected. You <i>don't know</i> whether or not you are a person who would respond to antiviral medication. How likely would you be to take antiviral medication if it were available to you for \$85 for the duration of the illness?	90%	50% (50%–100%)	75%	33%	Varied		f_T
0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%							

Table 2**Responses to Survey on Willingness-to-Pay**

Questionnaire Item	Median	Symbol	Interquartile Range
Imagine Mr. A and Mr. B. Neither is vaccinated against the avian flu. Mr. B catches avian flu, but Mr. A does not. Imagine that this winter you will experience either what Mr. A experienced in terms of health or what Mr. B experienced. How much would you be willing to pay to get Mr. A's experience rather than Mr. B's experience?	\$200	Translated to C_1	\$4950 (\$50–\$5000)
\$0, \$20, \$50, \$100, \$150, \$200, \$500, \$1000, \$5000, \$10,000, \$20,000, \$100,000			
Imagine that there is an avian flu pandemic, and prophylactic (preventative) antiviral medication is available to you, but you would have to pay for it yourself. What is the most money you would pay for a season's worth of the medication?	\$150	Used to estimate $C_{4,T}$ and $C_{4,P}^a$	\$450 (\$50–\$500)
\$0, \$20, \$50, \$100, \$150, \$200, \$500, \$1000, \$5000, \$10,000, \$20,000, \$100,000			
Imagine that instead of antiviral medication you could buy a prophylaxis (preventive measure) that is just as effective in preventing Avian flu but works like magic: no pills, no injection, no spray, no side effects, and no taking time out of your day to get it. What is the most money you would pay for this treatment?	\$200	Used to estimate $C_{4,T}$ and $C_{4,P}^a$	\$900 (\$100–\$1000)
\$0, \$20, \$50, \$100, \$150, \$200, \$500, \$1000, \$5000, \$10,000, \$20,000, \$100,000			

^aThe difference in willingness-to-pay (\$50) is used to estimate $C_{4,T}$ and $C_{4,P}$ because the symptoms for adverse effects associated with prophylaxis and treatment are similar.

Table 3

Description of Variables and Parameters

Notation	Description	Baseline Value	References
β_{SU}	Transmissibility of wild-type strain without antiviral treatment	0.30	[32–35]
β_{ST}	Transmissibility of wild-type strain with antiviral treatment	0.20 (=0.66* β_{SU})	[25,38]
β_R	Transmissibility of drug-resistant strain	0.27 (=0.9* β_{SU})	[25]
$1/\gamma$	Mean duration of infectiousness	4 days	[32–35]
α	Disease-related mortality	0.0178	[19]
ϕ	Coverage of prophylaxis	Varies	
e_p	Efficacy of prophylaxis in reducing susceptibility to the drug-sensitive strain	0.85	[25]
r_p	Probability of de novo resistance of prophylaxis	2×10^{-4}	[25]
f_T	Probability at which an individual chooses to use antivirals to treat his/her infection	Varies	
r_T	Fraction of treated individuals infected with drug-sensitive strains who acquire de novo resistance	2×10^{-3}	[25]
$1/\gamma_T$	Mean duration of infectiousness when treated	3 days	[25,38]
α_T	Disease-related mortality when treated	0.0051	[25,38]
S	Susceptible individuals		
S_p	Individuals who are on prophylaxis		
I_{SU}	Untreated individuals who are infected with a sensitive strain		
I_{ST}	Treated individuals who are infected with a sensitive strain		
I_R	Infected individuals with a resistant strain		
R	Individuals who are recovered from influenza		
$p(S)$	Probability that an infection is caused by the sensitive strain		
$p(R) = 1 - p(S)$	Probability that an infection is caused by the resistant strain		
$p(D)$	Probability of taking antivirals		
$p(REV)$	Probability of adverse effects when taking antivirals		
t_f	Duration of pandemic influenza		
C_1	Cost of the disease without treatment		
C_2	Cost of the disease with treatment		
$C_{3,T}$	Cost of antiviral treatment (drug costs)		
$C_{3,P}$	Cost of antiviral prophylaxis (drug costs)		
$C_{4,T}$	Cost of adverse effects associated with antiviral treatment		
$C_{4,P}$	Cost of adverse effects associated with antiviral prophylaxis		
$Q_{1,P}$	Expected cost of disease when on prophylaxis		
$Q_{1,T}$	Expected cost of disease when treated		
$Q_{2,P}$	Expected cost of disease without prophylaxis		
$Q_{2,T}$	Expected cost of disease without treatment		
AC_p	Average individual cost of disease when a proportion of population chooses to go on prophylaxis		
AC_T	Average individual cost of disease when a proportion of infected individuals seeks antiviral treatment		

Table 4**Infection Costs for Influenza Pandemic**

Outcome	Cost of Outcome (\$)	Probability (if infected and not treated)	Probability (if infected and treated)	References
Illness without medical care ^a	202	0.48	0.36	[33,55]
Outpatient visits ^a	330	0.52	0.31	[33,55]
Hospitalization ^a	6842	0.00144	0.00059	[55,56]
Mortality ^a	1,045,278	0.000480	0.000288	[55,57]
Average work loss (average, 1.9 days) ^a	336	1 (already estimated as average)	0.75	[58]
Cost of treatment ($C_{3,T}$)	85			[59]
Cost of prophylaxis ($C_{3,P}$)	454			[59]
Adverse effects for treatment (nausea for 2 days)	274 ($C_{4,T}$) ^b		0.11 ($P(REV_T)$)	[60,61]
Adverse effects for prophylaxis (nausea for 2 days)	274 ($C_{4,P}$) ^b		0.11 ($P(REV_P)$)	[60,61]

^aWeighted average of medical outcomes is used to estimate C_1 and C_2 .

^b0.0137 (QALY loss due to nausea for 5 days) * \$50,000 (societal willingness-to-pay per QALY) * 2 days/5 days = \$274.^{60,62,63} For sensitivity analysis, we also used different putative societal willingness-to-pay thresholds, \$75,000 and \$100,000 per QALY.