Original Article

The Optimal Allocation of Investment between Antivirals and Vaccines for Influenza Pandemic Preparedness Planning

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Objectives To investigate that given a fixed amount of financial resources, what is the optimal combination of vaccine and antiviral stockpiles in terms of minimizing the attack rate.

Methods Mathematic modeling was used to simulate the dynamics that with fixed influenza pandemic budget. Different budget conditions were observed if the combination changed. Framework between vaccines and antivirals was introduced by taking into account the uncertainty in vaccine and antiviral efficacy.

Results Given a fixed budget, different budget allocations between vaccines and antivirals stockpile gave different attack rates. When the price of vaccine was lower than or similar with the antivirals, the attack rate increased with increasing investment in antiviral. But if the price of the vaccine was higher than the antivirals, the attack rate may not decrease with increasing investment in vaccine. Fixed the vaccine effectiveness, higher effectiveness of antiviral got a lower attack rate. When both antiviral and vaccine were with 50% probability of effectiveness, the attack rate changed by antiviral stockpile with a same pattern as they were with 100% efficacy probability, even it has a higher attack rate.

Conclusions Assume the antivirals have 100% probability to be effective, budget was limited to a fix number, then in any event, population should stockpile a small amount of antivirals such that if the post-vaccination reproductive number turns out to be near 1, the additional intervention may further reduce the reproductive number to <1 and prevent the epidemic. Under the fixed budget, the price of the vaccines and antivirals will strongly affect the strategy of the stockpile allocation. When the price of vaccine is comparative lower, more investment of vaccine is better for the pandemic control, but if the vaccine price is too high then more investment in antiviral may be better. We found that attack rates and the optimal budget allocation depend on the probability to be effective of vaccine and antivirals.

Key words: Influenza pandemic; Preparedness; Allocation; Investment

Fuelled by the pandemic flu threat, the influenza preparedness research has developed rapidly in recent years. The H1N1 pandemic these years stimulates a further growth in this field. To control and mitigate the potential impact of influenza pandemic, interventions can be largely classified into non-pharmaceutical approaches such as personal sanitation habit, social distancing and infection control; and pharmaceutical approach such as the use of influenza vaccines and antivirals for treatment and prophylaxis.¹ Regulatory authorities have licensed pandemic vaccines in Australia, China and the United States of America, soon to be followed by Japan and several countries in Europe.²

Mathematical modeling can inform and optimize health policy decisions for how to make the optimal

stockpile for vaccination and antivirals.³ In the past 20 years, people used the mathematical modeling to evaluate the prediction of infectious disease and the effectiveness of prevention and treatment. The threat of pandemic influenza and the SARS in 2003 made the research in this field became active again. Several recent studies, based on mathematical modeling, have been proposed to translate the individual-level effects of vaccines and antiviral drugs into effectiveness of control strategies, and results showed that pre-pandemic vaccine has still been the optimal strategy.^{1,4-7} Riley et al found that lower individual doses might provide more benefits than few individuals with high dose of vaccine.⁸ Mylius et al showed that if a vaccine becomes available during the pandemic, when the number of new cases was close to its peak value, priority should be given to groups with a high-risk of developing complications. They also suggested that if the vaccine was available at the start, vaccinating

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school children would get a lower death rate.⁹ The research of Wu et al found that a small stockpile of a secondary antiviral drug could be used to prevent the adverse consequences of the emergence of antiviral-resistant pandemic influenza viruses.¹⁰

However, these studies above did not assess the optimal combination of vaccine and antiviral stockpiles to minimize the attack rate, given a fixed amount of financial resources. Thus, we conduct the present study to address this question. We will also search for how the vaccines and antivirals effectiveness influence to the influenza control.

METHODS

We assumed a new influenza pandemic happened in Hong Kong. The most possible strain is H5N1 avian influenza. We used vaccination to reduce the susceptibility to the infection and use antivirals to shorten the infectious period. The amount of vaccines and the antivirals would influence the attack rate of the pandemic and thus reduce the effect of the pandemic. We used various scenarios to find the smallest attack rate and the optimal stockpile ratio of vaccines and antivirals.

Modeling structure

We used the standard SIR compartmental modeling approach in our basic model.¹¹ Specifically, our model

Flowchart 1

is a modified version of the one used by Arinaminpathy N (Flowchart 1).¹² They changed the basic SIR model into two parts. Part of the people received the treatment and the others did not. They used a compartmental modeling approach to study the effect of the logistical constraints such as a finite stockpile of drugs and the limit on the distribution rate. The model did not include the condition that whether people have received vaccine and changed the susceptibility to the influenza infection or not. Based on this model, we assumed some fractions of the population are vaccinated for prophylaxis against pandemic influenza. The susceptibility of a vaccinated individual is reduced by a proportion $1 - \epsilon$. So we got the second model as shown in Flowchart 2. These two figures are the new models we developed to estimate the optimal allocation investment between antivirals and vaccines. The Variables and parameters were shown in Table 1.

The values of S, I_T, I_N are at time 0 and without vaccination. The values of $R_T, R_N, S_V, I_{VT}, R_{VT}, I_{VN}, R_{VN}$ varied with different budget allocation and different stockpile ratios of vaccines and antivirals. Following past studies on the 1918 pandemic, we assume an R_0 of 1.8. We assumed that while the antiviral stockpile was not empty, each infected individual received antiviral treatment with probability alpha.

Assumptions

We made the following assumptions in our model:

Flowchart 2

Table 1. Variables and parameters

Parameter symbol	Parameter discription	Value
S	susceptible to infection	7,000,000-30
I_T	no vaccination, infectious and receive treatment	30α
R_T	no vaccination, recovered after treatment and no longer susceptible	-
I_N	no vaccination, infectious and not receive treatment	$30(1-\alpha)$
R_N	no vaccination, recovered without treatment	-
S_V	vaccinated before time 0	-
I_{VT}	vaccinated but still infectious and receive treatment	-
R_{VT}	vaccinated but still infectious and recovered after treatment	-
I_{VN}	vaccinated but still infectious and not receive treatment	-
R_{VN}	vaccinated but still infectious, recovered without treatment	-
β	infectious per unit time/ infection rate	$1.8/4 = 0.45$
α	proportion of infected cases receiving treatment	0.4
f	f : force of infection (per capita rate at which susceptible are infected)	βI
γ	recovery rate	Vary with receiving treatment or not
ϵ	vaccine efficacy for susceptibility	0.15
N	the size of the population	7,000,000
$1/\gamma_T$	No vaccinated, recover in $1/\gamma_T$ days after receiving treatment	2.5
$1/\gamma_N$	No vaccinated, recover in $1/\gamma_N$ days without treatment	4
$1/\gamma_{VT}$	Vaccinated and receiving treatment, recover in $1/\gamma_{VT}$ days	2.5
$1/\gamma_{VN}$	Vaccinated and without treatment, recover in $1/\gamma_{VN}$ days	4
R_0	$R_0 = \beta/D_{IN}$	1.8

- a. We assumed a constant population size of 7 million (the size of Hong Kong) and ignored births and deaths.
- b. The population was homogeneous mixing and everyone had the same opportunity to contact with the infectious individuals. The infectious individuals were distributed randomly and without quarantine or isolation. We assumed that clinical patients were treated after onset of symptoms. We did not set the actual time of treatment. In reality, some cases would be diagnosed or reported late and some patients could not be correctly diagnosed or be prescribed drugs mistakenly. Thus only some of them (specified by the treatment probability α) received treatment.
- c. We assumed that the effect of vaccine was to reduce the susceptibility to the infection of influenza by a factor of $1 - \varepsilon$. We assumed that the effect of antiviral treatment was to reduce the infectious period, so that those who received treatment would recover in $1/\gamma_T$ days, and the people without treatment would recover in $1/\gamma_N$ days, where $\gamma_T > \gamma_N$. We followed Gani (2005) in assuming that the effect of antiviral treatment was to reduce the infectious period from 4 to 2.5 days. In other words, $\gamma_T = 0.4$, $\gamma_N = 0.25$.
- d. We did not consider any logistical delay in vaccination or antiviral treatment.
- e. We assumed that the product ability for vaccines and antiviral was enough for any possible budget.

Equations

Based on the model and the parameters and the above assumptions that we set above, we got the equations below:

$$\begin{aligned}\dot{S} &= \frac{dS}{dt} = -\beta(I_T + I_N + I_{VT} + I_{VN})S(t) \\ \dot{I}_T &= \alpha\beta(I_T + I_N + I_{VT} + I_{VN})S(t) - \gamma_T I_T \\ \dot{I}_N &= (1 - \alpha)\beta(I_T + I_N + I_{VT} + I_{VN})S(t) - \gamma_N I_N \\ \dot{R}_T &= \gamma_T I_T \quad \dot{R}_N = \gamma_N I_N \\ \dot{S}_V &= -\varepsilon\beta(I_{VT} + I_{VN} + I_T + I_N)S_V(t)\end{aligned}$$

$$\begin{aligned}\dot{I}_{VT} &= \varepsilon\alpha\beta(I_{VT} + I_{VN} + I_T + I_N)S_V(t) - \gamma_T I_{VT} \\ \dot{I}_{VN} &= \varepsilon(1 - \alpha)\beta(I_{VT} + I_{VN} + I_T + I_N)S_V(t) - \gamma_N I_{VN} \\ \dot{R}_{VT} &= \gamma_T I_{VT} \quad \dot{R}_{VN} = \gamma_N I_{VN} \\ f &= \beta(I_{VT} + I_{VN} + I_T + I_N) \\ 0 &\leq \alpha \leq 1\end{aligned}$$

Budget and efficacious parameters

We set a total budget B: $B = SA \times PA + SV \times PV$, where SA: antiviral stockpile; PA: antiviral price; SV: vaccine stockpile; PV: vaccine price; AR: attack rate; qv: probability that the vaccine is effective; qa: probability that the antiviral is effective.

RESULTS

AR changed with SA under different PV scenarios

Without loss of generality, we set the unit price of antiviral to be $PA = 1$. Likewise, the budget B and the vaccine price PV were both expressed in terms of the cost of antivirals. We took a price of vaccine between 0.5 and 3 and consider a budget of $B = 0.2$. A budget of 0.2 meant that there was enough fund to purchase antivirals for treating 20% of the population, which was consistent with the current amount that the United States had invested in its oseltamivir stockpile. Now given PA, PV and B, SV and SA are related by the equation $B = SA \times PA + SV \times PV$. Setting SA as the X axis and AR as the Y axis, Figure 1 shows 4 curves which correspond to the relationship between SA and AR under different vaccination price scenarios.

Illustration of different scenarios with the changing price of vaccine and the attack rates:

- a. When the price of vaccine was 0.5, if we put all the money on the vaccine ($SA = 0$), the attack rate would be 21%. But if we reserved a small amount of fund on the antiviral (e.g., $SA = 0.01$), the attack rate was reduced to 0. After that point, if we increased SA, the

Figure 1. The relationship between AR and SA for four different vaccine price.

Notes: 0.5 (blue), 1 (red), 2 (green), and 3 (purple). The budget is fixed at 0.2.

Figure 2. The relationship between AR and SA for four different vaccine price under different budgets.

Notes: (A) $B = 0.1$; (B) $B = 0.2$; (C) $B = 0.3$; (D) $B = 0.5$. The other parameters are the same with Figure 1.

attack rate would increase again. The reason for this unexpected trend was as follows: If the reproductive number (R) was less than 1, there would be no epidemic. If a proportion p of the population was vaccinated before the start of the outbreak, the reproductive number was reduced from R_0 to $R_0(1 - p)$. In our model, we have assumed that $R_0 = 1.8$, so to stop the epidemic we should vaccinate at least 44.4% of the population. If antiviral intervention was also implemented, the reproductive number dropped to $\beta[\alpha \times D_{IT} + (1 - \alpha) \times D_{IN}] \times (1 - p)$. Because $R_0 = \beta/D_{IN}$, $\beta = 1.8/4 = 0.45$. When $SA = 0$, no antiviral was available, so $\alpha = 0$ with $p = 0.4$. In this case, the reproductive number was 1.08 and the epidemic can occur with an attack rate of 21%. If SA was slightly above 0 with p just slightly below 0.4, we have $\alpha = 0.4$ and the reproductive number is $\beta[\alpha \times D_{IT} + (1 - \alpha) \times D_{IN}] \times (1 - p) = 0.648$, in which case the epidemic was halted and the attack rate was 0. As we increased SA further, SV would be less than 0.4 and p would decrease. From the equation: $\beta[\alpha \times D_{IT} + (1 - \alpha) \times D_{IN}] \times (1 - p)$ we could see that the reproductive number would increase. When

reduce the reproductive number below 1 regardless the reproductive number higher than 1, the epidemic would occur. This would explain the surprising shape of the blue curve. If the price of vaccination was more than 1.0, we could not of the antiviral stockpile size. Therefore, the attack rate was always greater than 0. From the figure we could find they were even higher than 50%.

b. When the vaccine price was 1.0, a larger antiviral stockpile would lead to an increase in attack rate (the red line).

c. When the vaccine price was 2.0, the relation between AR and SA was mostly flat (the green line). This line meant within the limitation of 0.2 budgets, the change of antiviral stockpile would not influence the attack rate if no more than 10% of population could receive the vaccine.

d. When the vaccine price was 3.0, which was 3 times higher than the antivirals' price, more antivirals stockpile was better because the attack rate decreased as SA increased.

PV influenced the AR under different budgets

Figure 2 showed that if we kept the same parameters and changed the budget to be 0.1, 0.3, and 0.5, higher PV resulted in a lower SV and then lead to a higher AR. If the investment could provide more than 44.44% of vaccination in the whole population, no matter what the SA was, the AR would always less than 0. Until we reduced

Table 2. Four scenarios of antiviral and vaccine effective (w.p.-with probability)

	Vaccine effective	Vaccine not effective
AV effective	Scenario A	Scenario B
	w.p. $qa \times qv$	w. p. $qa \times (1 - qv)$
AV not effective	Scenario C	Scenario D
	w.p. $(1 - qa) \times qv$	w. p. $(1 - qa) \times (1 - qv)$

Note: AV: antiviral.

the investment in vaccines and correspond to add the investment in SA to more than 0.1, the AR will more than 0. The epidemic would occur. That means: if the vaccines have 100% probability to be efficacious and we have as much as budget then we may not need antivirals. However, this is only an idealism condition.

AR influenced by different q_a and q_v match scenarios

In the above conditions, we assumed that both the vaccine and antiviral were effective against the pandemic virus (as for seasonal influenza). But in reality, because the pandemic strain could not be observed before the pandemic stroke and people may have resistance to the antivirals, the efficacy of vaccine and antiviral were not guaranteed. They might not have 100% probability to be effective. In the simplest case, four possible scenarios were shown in Table 2.

We used q_v to denote the probability that the vaccine was effective. If the vaccine was not effective (with probability $1 - q_v$), then ε (reduction in susceptibility after the vaccination) = 1. If the vaccine was effective (with probability q_v), $\varepsilon = 0.15$. We used q_a to denote the probability that the antiviral was effective. When the antiviral was effective (with probability q_a), the average infectious duration of treated individuals was D_{IT} days. Otherwise, the antiviral was not effective (with probability $1 - q_a$), and the average infectious duration of treated individuals was the same as untreated individuals, i.e. D_{IN} days.

a. In scenario A, both the vaccine and the antiviral were effective, which occurred with probability $q_v \times q_a$. In this scenario, $\text{Epsilon} = 0.15$ and the average infectious duration of treated cases was D_{IT} .

b. In scenario B, the antiviral was effective but the vaccine was not effective, which occurred with probability $(1 - q_v) \times q_a$. In this scenario, $\text{Epsilon} = 1$ and the average infectious duration of treated cases was D_{IT} .

c. In scenario C, the antiviral was not effective but the vaccine was effective, which occurred with probability $(1 - q_a) \times q_v$. In this scenario, $\text{Epsilon} = 0.15$ and the average infectious duration of treated cases was D_{IN} .

d. In scenario D, both the antiviral and the vaccine were not effective, which occurred with probability $(1 - q_v) \times (1 - q_a)$. In this scenario, $\text{Epsilon} = 1$ and the average infectious duration of treated cases was D_{IN} .

The expected attack rate was obtained by averaging the attack rates in these four scenarios. This could be described by the equation below:

$E[AR] = E[AR|a] p(a) + E[AR|b] p(b) + E[AR|c] p(c) + E[AR|d] p(d)$, where $p(a) = q_a \times q_v$, $p(b) = q_a \times (1 - q_v)$, $p(c) = (1 - q_a) \times q_v$, $p(d) = (1 - q_a) \times (1 - q_v)$ Equation (aa).

Now we tried to change q_a and q_v and observed the change of the attack rate:

a. When $q_v = 1$, AR change with q_a : When $q_v = 1$, we

let q_a varied between 0 and 1 ($q_a = 0, 0.25, 0.5, 0.75, 1$) and calculated the corresponding attack rate to help us understand how q_a influenced the attack rates. When $q_v = 1$, the equation (aa) changed to:

$E[AR] = E[AR|a] q_a + E[AR|c] (1 - q_a)$.

In this scenario, $E[AR|a]$ was the attack rate when both vaccine and antiviral work and people received treatment recovered in D_{IT} days (by γVT). $p(a)$ was $q_a \times \text{Epsilon} = 0.15$. $E[AR|c]$ was the attack rate when vaccine had 100% efficacy probability and people who received treatment but still recovered in D_{IN} (by γVN). $p(c)$ was $(1 - q_a)$. We changed q_a varied from 0 to 1 and got the corresponding AR. In this scenario, we still set $B = 0.2$, and $PA = 1.0$, $PV = 1.0$ (Figure 3).

b. When $q_a = 1.0$, AR changed with q_v (Figure 4):

When $q_a = 1.0$, the equation (aa) changed to: $E[AR] = E[AR|a] q_v + E[AR|b] (1 - q_v)$.

c. When $q_v = 0$, AR changed with q_a (Figure 5):

When $q_v = 0$, the equation (aa) changed to: $E[AR] = E[AR|b] q_a + E[AR|d] (1 - q_a)$.

The higher q_a , the lower attack rate was observed.

The attack rate decreased with increasing antivirals stockpile when the antivirals efficacy was more than 0. When the vaccine was not effective, the attack rate did not change with the increasing antiviral stockpile. It showed as a parallel line. The attack rate will always be 73%.

d. When $q_a = 0$, AR changed with q_v (Figure 6):

When $q_a = 0$, the equation (aa) changed to: $E[AR] = E[AR|c] q_v + E[AR|d] (1 - q_v)$. The higher vaccine efficacy probability, the lower the attack rate was. With same q_v , the attack rate increases as the antivirals stockpile increases.

e. New framework of probabilistic structure

In all the above scenarios, we first set q_v or q_a as 1.0 and then changed the value of corresponding q_a or q_v . How about the results of the middle value of different q_a matched with middle value of different q_v ? When $q_a = 0.5$ and $q_v = 0.5$, the equation (aa) changed to: $E[AR] = E[AR|a] 0.5 \times 0.5 + E[AR|b] 0.5 \times 0.5 + E[AR|c] 0.5 \times 0.5 + E[AR|d] 0.5 \times 0.5$.

In this scenario, $E[AR|a]$ was the expected AR when $\text{epsilon} = 0.15$ and the recovery time was D_{IT} ; $E[AR|b]$ was the expected AR when $\text{epsilon} = 1$ and the recovery time was D_{IT} ; $E[AR|c]$ was the expected AR when $\text{epsilon} = 0.15$ and the recovery time was D_{IN} ; $E[AR|d]$ was the expected AR when $\text{epsilon} = 1.0$ and the recovery time was D_{IN} ; After calculated, we got the corresponding AR. Then we got a new figure using the same parameter as before. In the new figure, we matched $q_a = 0, 0.5$ and 1 and $q_v = 0, 0.5$ and 1 to each other and got 9 lines.

Table 3. Different q_a matched with q_v

q_a	q_v		
	0	0.5	1.0
0	EAR-A0V0	EAR-A0V0.5	EAR-A0V1.0
0.5	EAR-A0.5V0	EAR-A0.5V0.5	EAR-A0.5V1.0
1.0	EAR-A1.0V0	EAR-A1.0V0.5	EAR-A1.0V1.0

Figure 3. When $qv = 1.0$, the attack rate is influenced by qa (vary from 0 to 1.0).

Notes: EAR-A0 is the expected attack rate when $qa = 0$. Similarly, EAR-A1.0 is the expected AR when $qa=1.0$. The higher qa , the lower attack rate. With the same qa , AR increases as SA increases.

Figure 4. When $qa=1$, AR was influenced by qv (vary from 0 to 1.0).

Notes: EAR-V0 was the expected attack rate when $qv=0$. Similarly, EAR-V1.0 was the expected AR when $qv = 1$. The higher qv , the lower attack rate. The attack rate increased with antivirals stockpile increasing when $qv < 0.5$; the attack rate decreased with i antivirals stockpile ncreasing when the $qv > 0.5$; the attack rate did not change with the increase of antiviral stockpile when $qv = 0.5$

Figure 5. $qv = 0$, AR influenced by qa (vary from 0 to 1.0).

Notes: EAR-A0 is the expected attack rate when $qa = 0$. Similarly, EAR-A1.0 is the expected AR when $qa = 1$.

Figure 6. $q_a = 0$, AR influenced by q_v (vary from 0 to 1.0).

Notes: EAR-V0 is the expected attack rate when $q_a = 0$. Similarly, EAR-V1.0 is the expected AR when $q_a = 1$.

Figure 7. AR changes with SA by different matches of q_a & q_v .

Notes: EAR-A0V0 is the expected AR when $q_a = 0$ and $q_v = 0$. Similarly, EAR-A0.5V0.5 is the expected AR when $q_a = 0.5$ and $q_v = 0.5$. EAR-A1.0V1.0 is the expected AR when $q_a = 1$ and $q_v = 1$.

Table 3 shows how the q_a was matched with q_v . In this table, the EAR-A0V0 was the expected AR when $q_a = 0$ and $q_v = 0$. Similarly, EAR-A0.5V0.5 was the expected AR when $q_a = 0.5$ and $q_v = 0.5$. EAR-A1.0V1.0 was the expected AR when $q_a = 1$ and $q_v = 1$.

Figure 7 shows that:

- When both antiviral and vaccine had 100% probability to be effective, we got the lowest attack rate.
- Neither antiviral nor vaccine had any probability to be effective if we got the highest attack rate.
- When both antiviral and vaccine had 50% probability to be effective, the line of AR changed by SA had the efficacy probability. But the AR in every SA point was higher than the 100% q_a and q_v same grade with the line that they both have 100% efficacy probability.

But the AR in every SA point was higher than the 100% q_a and q_v .

d. Fixed the q_v , higher q_a corresponded to the lower AR.

e. Fixed the q_a , higher q_v corresponded to the lower AR.

DISCUSSION

Consistent with the previous models, we found that higher total budget would lead to a lower AR when both q_a and q_v were 1.0. When the budget was high enough and could provide more than $(1-1/R_0)$ of the total population to get vaccination, the epidemic may not happen. But in reality, it was impossible to guarantee that the vaccine would be effective (i.e. $q_v < 1$). One of the most important findings from our modeling is: given a fixed budget, different budget allocations

between vaccines and antiviral gave different attack rates. If the antivirals and the vaccines were both effective with a probability as 1, population should stockpile a small amount of antivirals in any situation. If the post-vaccination reproductive number turned out to be slightly above 1, the additional antiviral intervention may further reduce the reproductive number to < 1 and prevent the epidemic.

When assessing the effect of different budget allocations on the attack rate, we fixed the price of antivirals and varied the price of the vaccine. We found that under the fixed budget, the price of the vaccine would strongly affect the strategy of the stockpile allocation. When the price of vaccine was lower than or similar with the antivirals (i.e. $PV < 1$), increased investment of vaccine was good for the pandemic control, because AR would increase with higher investment in antiviral when the budget was fixed. But if the price of the vaccine was high ($PV = 2.0$ or $PV = 3.0$), improved investment on the vaccine may not benefit for the influenza pandemic control. As in figure 4, the line may be parallel, descent or curve. The AR may not change with the increase of SA.

In present study, we provided a new framework for influenza pandemic budget allocation between vaccines and antivirals by taking into account the uncertainty of vaccines and antivirals efficacy (via q_a and q_v). Obviously, our framework can be made more realistic by using a more complex probabilistic structure (e.g. a continuous spectrum for q_a and q_v between 0 and 1). We found that both attack rate and the optimal budget allocation depended on q_v and q_a . When we fixed the q_v , higher q_a would lead to a lower AR. Likewise, when we fixed q_a , higher q_v would lead to a lower AR. When both antiviral and vaccine had 100% probability to be effective, we got the lowest attack rate. If neither antiviral nor vaccine had any probability to be effective, we got the worst result of control. When both antiviral and vaccine had 50% probability to be effective, the line of AR changed by SA had the same grade with the line that they both have 100% efficacy probability. But the AR in every SA point was higher than the 100% q_a and q_v . So the control result would be worse.

Strengths and limitations

The model used basic model's assumption of homogeneous mixing. This is a Stochastic SEIR meta-population model. It was a simple model structure. If we used heterogeneous subgroup mixing, we need to include age and spatial structure, which would make the model more complicate and hard to interpret. To the best of our knowledge, there is no mathematic modeling study on investigating how to optimally allocate resources between vaccine and antivirals for influenza pandemic preparedness. Our study for the first time introduced a useful modeling framework to public health officials. We also considered for

different scenarios including different prices of vaccine and antiviral as well as the probabilities that these medications were effective. Specifically, we believe that when allocating limited resources, it is very important to take into account the effectiveness of vaccine or antiviral.

However, there are still several limitations needed to be mentioned. First of all, we assumed homogeneous mixing and did not consider any explicit spatial structure. In fact, the susceptibility and the infectious force and recovery rate would be variable between different age and social groups. Then we assumed that transmission was always with the same R_0 in our entire simulation. In actual, the R_0 would change to R when the pandemic develops, and the infectious force might change with time going.

Secondly, for simplicity, we assumed that if the vaccine matches the pandemic virus, no matter what the match probability was, the influence to the reduction of susceptibility was the same ($\epsilon = 0.15$), but in fact the probability and ϵ may be correlated. Thirdly, we only assumed that the effect of antiviral treatment was to reduce the infectious period and the effect of vaccine was to reduce the susceptible to the infection of influenza virus. However, the antivirals may also provide the effect of prevention, and the vaccines may also influence infectious period. Furthermore, we did not consider the stockpile loss in the process of transportation or preservation. Future studies are warranted to consider these aspects.

Our model helps people to address the best economic effect for the influenza control work. Our results suggest that the government, especially those in the developing countries should pay more attention to the work for vaccine and antiviral stockpile, and the cost-effectiveness of resources allocations to effectively control and prevent the development of influenza pandemic.

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