Modeling the impact of air, sea, and land travel restrictions supplemented by other interventions on the emergence of a new influenza pandemic virus

Technical Appendix

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1. Mathematical model formulation

Basic stochastic $SEIR$ model

The model applied the concept of binomial chain process [1, 2] and the similar notation as Lekone (2006) [3]. Let $\Delta t$ be a time step and $(t, t + \Delta t]$ be a time interval, we denote $S(t), E(t), I(t),$ and $R(t)$ as the number of individuals in Susceptible, Exposed, Infected, and Recovered compartments at time $t$, respectively. Suppose $B(t)$ is the incidence, the number of susceptible getting infected and $C(t)$ is the number of infected individuals who start to be infectious at time $t$. And $D(t)$ is the number of individuals recovered or died
from infectious state at time $t$. Suppose the population is homogeneously mixed, the system of general SEIR stochastic model with no intervention is

$$
S(t + \Delta t) = S(t) - B(t) \\
E(t + \Delta t) = E(t) + B(t) - C(t) \\
I(t + \Delta t) = I(t) + C(t) - D(t) \\
R(t + \Delta t) = R(t) + D(t)
$$

(1)

An individual would have a probability $p$ to get into next stage which follows a bernoulli distribution. So given $n$ individuals, the number of individuals who get into next stage would follow a binomial distribution with probability $m$. We take $\text{bin}(m, n)$ as a binomial distribution with parameters probability $m$ and number of total individuals $n$. The corresponding distributions for the classes

$$
B(t) \sim \text{bin}(1 - \exp[-\beta I(t)\Delta t], S(t)) \\
C(t) \sim \text{bin}(1 - \exp(-\alpha \Delta t), E(t)) \\
D(t) \sim \text{bin}(1 - \exp(-\gamma \Delta t), I(t))
$$

(2)

where the rate of infection is equal to $\beta I(t)/N$ for a time step, $\beta$ is the transmission rate, and $N$ is the population size. The $\alpha$ and $\gamma$ are the constant transition rates from latent state to infectious state and from infectious state to removed state respectively. And the rates are transformed into probabilities assuming in poisson process.
**Arrived and departed cases**

Suppose the probabilities of travel are the same for all individuals and the probability of travelers imported from country $i$-th ($i = 1, 2, ..., p$) are represented by $m_{k,i}^I$ by means of transport $k$ ($k = 1, 2, 3$) for air, sea, and land respectively. The daily probability of travel $m_{k,i}^I$ for an individual is calculated by $\frac{\text{total frequency of travel by transport } k \text{ in a year}}{365 \times \text{population } N_i}$. The arrival statistics listed in Table 1 are adopted from the Hong Kong Tourism Board. We used the most up-to-date available statistics (i.e. data in 2007) [4]. The statistics include the total number of visitor arrivals by countries with the mode of transports: air, sea, and land.

Here are the model compartments of imported cases in latent status,

$$ IM_k^E(t) = \sum_{i=1}^{p} \binom{m_{k,i}^I, E_i(t)} $$ (3)

and infectious status,

$$ IM_k^I(t) = \sum_{i=1}^{p} \binom{m_{k,i}^I, I_i(t)} $$ (4)

The number of latent subjects, $E_i(t)$, and the number of infectious subjects, $I_i(t)$, at time $t$ of country $i$-th are generated from discrete-time $SEIR$ model based on the reproduction numbers of the countries,
Table 1. Frequency of departures and arrivals by countries with the modes of transports in 2007

| Country         | Mode of transport | Departure         | Arrival       |
|-----------------|-------------------|-------------------|---------------|
|                 |                   | Total             | Air           | Sea           | Land           |
| **Departure**   |                   | 80,682,000        | 6,141,000     | 8,871,000     | 65,670,000     |
| Hong Kong       |                   | 1,230,927         | 724,023       | 191,178       | 315,726        |
| **Arrival**     |                   | 395,167           | 219,469       | 59,004        | 116,694        |
| Canada          |                   | 1,662             | 675           | 225           | 762            |
| Honduras        |                   | 35,706            | 21,260        | 5,821         | 8,625          |
| Mexico          |                   | 10,515            | 5,690         | 1,805         | 3,020          |
| Brazil          |                   | 40,339            | 19,861        | 8,061         | 12,417         |
| Venezuela       |                   | 10,896            | 4,356         | 1,612         | 4,928          |
| United Kingdom  |                   | 601,168           | 448,647       | 68,007        | 84,514         |
| Netherlands     |                   | 110,816           | 70,592        | 15,712        | 24,512         |
| Denmark         |                   | 30,013            | 18,734        | 4,193         | 7,086          |
| Finland         |                   | 21,830            | 13,365        | 3,448         | 5,017          |
| Norway          |                   | 18,624            | 12,381        | 2,327         | 3,916          |
| Sweden          |                   | 49,810            | 30,909        | 7,449         | 11,452         |
| Austria         |                   | 24,046            | 14,514        | 4,529         | 5,003          |
| Germany         |                   | 234,763           | 149,370       | 38,523        | 46,870         |
| Switzerland     |                   | 46,870            | 32,529        | 6,561         | 7,780          |
| France          |                   | 231,091           | 135,291       | 41,515        | 54,285         |
| Belgium         |                   | 32,413            | 20,190        | 5,114         | 7,109          |
| Italy           |                   | 118,841           | 73,043        | 17,564        | 28,234         |
| Portugal        |                   | 18,639            | 9,419         | 8,199         | 1,021          |
| Spain           |                   | 65,131            | 38,460        | 10,757        | 15,914         |
| Russia          |                   | 32,858            | 21,256        | 4,314         | 7,288          |
| South Africa    |                   | 72,897            | 47,001        | 4,357         | 21,539         |
| Bahrain         |                   | 2,500             | 1,833         | 106           | 561            |
| Egypt           |                   | 16,361            | 7,764         | 579           | 8,018          |
| Israel          |                   | 63,435            | 38,692        | 9,537         | 15,296         |
| Jordan          |                   | 11,084            | 4,809         | 333           | 5,942          |
| Kuwait          |                   | 4,366             | 2,838         | 283           | 1,245          |
| Saudi Arabia    |                   | 19,435            | 13,616        | 787           | 5,032          |
| Turkey          |                   | 41,011            | 20,619        | 2,764         | 17,628         |
| United Arab Emirates | 11,881 | 9,358 | 615 | 1,908 |
| Australia       |                   | 633,599           | 418,760       | 83,173        | 131,666        |
| New Zealand     |                   | 117,215           | 82,461        | 10,762        | 23,992         |
| Japan           |                   | 1,324,336         | 748,478       | 273,334       | 302,524        |
| South Korea     |                   | 876,231           | 507,872       | 136,095       | 232,264        |
| Indonesia       |                   | 366,217           | 185,197       | 63,102        | 117,918        |
| Malaysia        |                   | 504,487           | 237,542       | 105,036       | 161,909        |
| Philippines     |                   | 552,942           | 365,490       | 70,956        | 116,496        |
| Singapore       |                   | 631,963           | 393,423       | 93,794        | 144,746        |
| Thailand        |                   | 387,219           | 246,732       | 47,800        | 92,687         |
| India           |                   | 317,510           | 178,018       | 33,588        | 105,904        |
| Taiwan          |                   | 2,238,731         | 1,248,228     | 123,793       | 866,710        |
| Macau           |                   | 626,103           | 30,547        | 553,682       | 41,874         |
| China           |                   | 15,485,789        | 2,069,683     | 1,618,643     | 11,797,463     |
\[ E_i(t + \Delta t) = E_i(t) + S_i(t)[1 - \exp(-\beta_i \Delta t I_i(t)/N_i)] - E_i(t)[1 - \exp(-\alpha \Delta t)] \]

\[ I_i(t + \Delta t) = I_i(t) + E_i(t)[1 - \exp(-\alpha \Delta t)] - I_i(t)[1 - \exp(-\gamma \Delta t)] \]

(5)

where \( 1 - \exp(-\beta_i \Delta t I_i(t)/N_i) \), \( 1 - \exp(-\alpha \Delta t) \), and \( 1 - \exp(-\gamma \Delta t) \) are the per capita probabilities of infection, becoming infectious, and becoming recovered respectively given transmission parameter \( \beta_i \) in population \( N_i \). Individual transmission parameter \( \beta_i \) is calculated from the basic reproduction number \( (R_0) \) of country \( i \)-th. It is defined as the average number of secondary infections produced by a typical infected individual in a wholly susceptible population. In order to allow the transmission heterogeneities between non-local countries, we will estimate the reproduction numbers by the initial exponential growth rate method [5] employing two months after dates of their first onset cases (which showed in Table 2) daily surveillance data [6] [7] [8],

\[ R_0 = 1 + \frac{r^2 + (\alpha + \gamma)r}{\alpha \gamma} \]

(6)

where \( r \) is the initial exponential growth rate estimated by the least square fitting to the model, i.e. \( \log(\text{cumulative number of cases at time } t) \propto rt \).

At the same time, a number of infected individuals will leave and carry the pathogens away from the local city. Departure statistics are collected from the Census and Statistics Department, Hong Kong [9] and are listed in Table 1. Let \( m_k^E \) be the probability of departure from local area by the mode of transport \( k \), the compartments of exported cases
in latent status, $EX^E(t)$, and in infectious status, $EX^I(t)$, will be $\sum_{k=1}^{3} bin(m_k^E, E(t))$ and $\sum_{k=1}^{3} bin(m_k^I, I(t))$ respectively. The calculation of $m_k^E$ is similar to that of $m_k^I$, which adapts the departure data in Table 1.

**Result of estimated $R_0$ and corresponding confidence interval (CI)**

The reproduction numbers of the forty-four non-local countries are estimated by the initial exponential growth rate method. All of the initial growth rates are fitted significantly ($p-value < 0.05$). Showed in Table 2, the $R_0$ range from 1.1 to 1.9.

**Antiviral and hospitalization**

Two new compartments are added into the model, antiviral Treatment $T(t)$ and Hospitalization $H(t)$. Once individuals become infectious, they seek for antiviral treatment and hospitalization with proportions $p_T$ and $p_H$ respectively. With regard to limited resources, part of them may be untreated as proportions $p_U$. We adapt a $\psi$ fraction reduction of infectiousness for individuals who receive antiviral. Suppose classes $M(t)$ and $N(t)$ are the number of infectious individuals who take antiviral treatment and hospitalization at time $t$ respectively. The $P(t)$ and $Q(t)$ are the number of removed individuals from antiviral treatment and hospitalization with transition rates $\gamma_T$ and $\gamma_H$ to the removed status.

**Stochastic SEIR model with interventions**

Because infectious individuals include those being treated and hospitalized, the probability of a susceptible person becoming infected is equal to $1 - exp[\beta[I(t) + (1-\psi)T(t)+H(t)]/N]$ for a time step $\Delta t$. Given $\nu$ is the sensitivity of the entry screening board, so only $\nu$ proportion of imported infectious individuals are able to be identified as positive cases.
| Country          | Start date MM/DD | $R_0$ (CI)   |
|-----------------|------------------|--------------|
| United States   | 04/21            | 1.62 (1.52, 1.72) |
| Canada          | 04/28            | 1.42 (1.38, 1.47) |
| Honduras        | 05/23            | 1.39 (1.31, 1.48) |
| Mexico          | 03/11            | 1.56 (1.52, 1.59) |
| Argentina       | 05/09            | 1.81 (1.73, 1.90) |
| Brazil          | 05/09            | 1.45 (1.42, 1.49) |
| Venezuela       | 05/29            | 1.43 (1.37, 1.49) |
| United Kingdom  | 04/28            | 1.51 (1.47, 1.54) |
| Netherlands     | 05/01            | 1.42 (1.38, 1.47) |
| Denmark         | 05/02            | 1.37 (1.32, 1.42) |
| Finland         | 05/13            | 1.32 (1.30, 1.35) |
| Norway          | 05/11            | 1.27 (1.26, 1.28) |
| Sweden          | 05/07            | 1.39 (1.37, 1.41) |
| Austria         | 04/30            | 1.24 (1.20, 1.27) |
| Germany         | 04/30            | 1.37 (1.34, 1.39) |
| Switzerland     | 05/01            | 1.38 (1.35, 1.41) |
| France          | 05/02            | 1.33 (1.31, 1.35) |
| Belgium         | 05/14            | 1.24 (1.23, 1.26) |
| Italy           | 05/03            | 1.29 (1.27, 1.31) |
| Portugal        | 05/06            | 1.24 (1.21, 1.27) |
| Spain           | 04/28            | 1.30 (1.25, 1.35) |
| Russia          | 05/23            | 1.06 (1.04, 1.08) |
| South Africa    | 06/18            | 1.69 (1.62, 1.76) |
| Bahrain         | 05/27            | 1.35 (1.31, 1.40) |
| Egypt           | 06/03            | 1.35 (1.30, 1.40) |
| Israel          | 04/29            | 1.42 (1.39, 1.45) |
| Jordan          | 06/17            | 1.26 (1.23, 1.30) |
| Kuwait          | 05/25            | 1.10 (1.09, 1.11) |
| Saudi Arabia    | 06/03            | 1.48 (1.43, 1.54) |
| Turkey          | 05/17            | 1.30 (1.27, 1.32) |
| United Arab Emirates | 05/25        | 1.30 (1.25, 1.34) |
| Australia       | 05/09            | 1.87 (1.77, 1.98) |
| New Zealand     | 04/29            | 1.35 (1.30, 1.41) |
| Japan           | 05/09            | 1.44 (1.35, 1.53) |
| South Korea     | 05/03            | 1.43 (1.39, 1.46) |
| Indonesia       | 06/24            | 1.69 (1.62, 1.75) |
| Malaysia        | 05/16            | 1.59 (1.54, 1.64) |
| Philippines     | 05/22            | 1.66 (1.60, 1.71) |
| Singapore       | 05/27            | 1.58 (1.53, 1.64) |
| Thailand        | 05/14            | 1.80 (1.71, 1.88) |
| India           | 05/17            | 1.56 (1.51, 1.60) |
| Taiwan          | 05/20            | 1.28 (1.23, 1.32) |
| Macau           | 06/19            | 1.39 (1.34, 1.45) |
| China           | 05/12            | 1.52 (1.50, 1.55) |
and be voluntary quarantined. Let $f_k$ be the restriction fraction for import transportation $k$-th, the stochastic system is as follow,

\[
S(t + \Delta t) = S(t) - B(t)
\]
\[
E(t + \Delta t) = E(t) + B(t) + \sum_k (1 - f_k) IM_k^E(t) - EX^E(t) - C(t)
\]
\[
I(t + \Delta t) = I(t) + C(t) + (1 - \nu) \sum_k (1 - f_k) IM_k^I(t) - EX^I(t) - D(t) - M(t) - N(t)
\]
\[
T(t + \Delta t) = T(t) + M(t) - P(t)
\]
\[
H(t + \Delta t) = H(t) + N(t) - Q(t)
\]
\[
R(t + \Delta t) = R(t) + D(t) + P(t) + Q(t)
\]

(7)

The distributions for the classes are

\[
B(t) \sim \text{bin}(1 - \exp[-\beta N(I(t) + (1 - \psi)T(t) + H(t)]\Delta t]), S(t))
\]
\[
C(t) \sim \text{bin}(1 - \exp(-\alpha \Delta t), E(t))
\]
\[
M(t) \sim \text{bin}(p_T \Delta t, I(t))
\]
\[
N(t) \sim \text{bin}(p_H \Delta t, I(t))
\]
\[
D(t) \sim \text{bin}(p_U [1 - \exp(-\gamma_R \Delta t)], I(t))
\]
\[
P(t) \sim \text{bin}(1 - \exp(-\gamma_T \Delta t), T(t))
\]
\[
Q(t) \sim \text{bin}(1 - \exp(-\gamma_H \Delta t), H(t))
\]

(8)
The descriptions of the parameters are highlighted in Table 3. A simple schematic flow is showed in Figure 1.

**Table 3. Parameters, definitions, and values for the model**

| Parameter | Definition | Value | Ref/remarks |
|-----------|------------|-------|-------------|
| $R_0$     | Basic reproductive number | Estimated | Local baseline estimated about 1.4 |
| $T_E = 1/\alpha$ | Average latent period (days) | 1.45 | [11] [12] |
| $T_I$     | Average infectious period (days) | 2.9 | [11] [12] |
| $T_T$     | Average infectious period (days) | 1.4 | [13] |
|           | for individuals treated with antiviral treatment |   | |
| $T_H$     | Average infectious period (days) | 1.4 | [13] |
|           | for hospitalized individuals |   | |
| $p_T$     | Proportions of infectious subjects selected for treatment | 0.12 | [14] |
| $p_H$     | Proportions of infectious subjects selected for hospitalization | 0.06 | [15] |
| $p_U$     | Proportions of untreated infectious subjects | $1 - p_T - p_H$ |   |
| $\gamma_R$ | Transition rates from infectious state to removed state | $1/T_I$ |   |
| $\gamma_T$ | Transition rates from treatment state to removed state | $1/T_T$ |   |
| $\gamma_H$ | Transition rates from hospitalization state to removed state | $1/T_H$ |   |
| $f_k$     | Restriction fraction for $k$-th transportation | 90%, 99% | Assumption |
| $\psi$    | Fraction of infectiousness reduction for antiviral treatment | 60% | [16] |
| $\nu$     | Sensitivity of the screening board for infectious subjects | 0.3 | [10] |
Figure 1. Schematic flow of SEIR model which incorporated the compartments treatment and hospitalization with import-export latent and infectious individuals

Epidemic evolution

The pandemic is seeded according to the start dates (Table 2) of each country [6] [7]. The earliest epidemic was seeded in Mexico on March 11, 2009 [8]. Each country will develop its own infected cases by generating from the discretized-time SEIR model based on the estimated reproduction number. At the same time, the countries will send their infected cases to Hong Kong and the local epidemic evolution will be initiated by the successive imported cases via air, sea, and land traffic. The first passage times (FPT), first one hundred passages times (FHPT), and the peak time are calculated for different restriction strategies.

Baseline scenario

Since the Hong Kong Government confirmed the first imported case of H1N1pdm on May 1, 2009 [17], the parameters $E_i(0)$ and $I_i(0)$ are roughly assumed the same for all countries and are iteratively estimated, thereby minimizing the difference between the reported
date and the simulated first passage time (FPT). Allowing for stochastic variability, the baseline transmission rate ($\beta$) is fitted using the local surveillance data for the first two months following the day of the first local import, in the absence of travel restrictions and intervention. Local daily surveillance of confirmed infected cases (Figure 2) was available from press releases on human swine flu, published by the Department of Health, Hong Kong [18]. Optimum parameter is chosen which had average minimum relative mean square error between empirical and estimated cumulative incidence by Monte Carlo simulation. The reproduction number is the product of the transmission rate and the average infectious period. We adapt the range of parameter space for the reproduction numbers according to previous influenza A (H1N1) studies [8] [11] [19] [20].

**Result of baseline estimation**

The estimated parameters $E_i(0)$ and $I_i(0)$ are equal to 90 individuals which obtain May 4 as a mean FPT with a 95% confidence interval [Apr 14, May 16]. The local estimated $R_0$ is about 1.4 during the first two months after the reported FPT. The fitted cumulative incidence curve from data was showed in Figure 2.

**Computer simulation**

The model is implemented in software SAS 9.1.3. Simulation is started by the first global onset case with one day time step. The program generates one hundred realizations for each scenario. The medians, means, and the 95% non-parametric confidence intervals of the incidence, peak times, and the time of imported case arrivals are calculated over the realizations among different scenarios.
Figure 2. Daily confirmed cases in Hong Kong and the median curve simulated from the best fitted model. The confirmed cumulative cases (the grey bar in the figure) is from the press releases on human swine flu, published by the Department of Health, Hong Kong. The median cumulative cases (the dash line) were simulated by 100 realizations from the best fitted model.
2 Impact of other variations

Variations of $R_0$ from non-local countries

We varied the $R_0$s from 44 foreign countries by 20%, in order to test these effects on our results. The increased and decreased $R_0$s ranged from 1.3 to 2.2 (median 1.7), and from 0.8 to 1.5 (median 1.1), respectively. Although five countries did not occur any outbreak i.e. $R_0 < 1$, it made small impact on the size of infected cases exportation among all countries.

Showed in Figure 3, the external travel restrictions performed slightly better in deferring the FPTs and the FHPTs when the $R_0$s from non-local countries decreased. Given the $R_0$s increased by 20%, the medians of FPT and the FHPT were day 44-th and day 74-th respectively with no travel restriction; the medians of FPT and the FHPT were day 63-th and day 112-th respectively when the $R_0$s decreased 20%. Amongst all situations for the changes of the $R_0$s, either 90% or 99% of air travel rescaling could have about 1 week delay for the FPTs; but once all means of transport were 90% or 99% restricted, the FPT would have one month more delay when the $R_0$s decreased 20% compared to that of the $R_0$s with 20% increases. Moreover, the FHPT could be delayed for more than 2.5 months with 20% decreases of the $R_0$s, whereas the FHPT was delayed for 1.5 months with 20% increases of the $R_0$s for a 99% restriction of all means of transport.

Since the number of imported cases depended on the changes of the $R_0$ from the non-local countries, the growth of the local epidemic was affected by the cases passage times (Figure 4). When the $R_0$s increased by 20%, the five months’ cumulative AR attained 19% and the epidemic ended at the seventh month since the first global case arose. During the first five months, the blockings of all external means of transport were still effective on controlling the cumulative ARs. A 99% travel restriction maintained about 12% of seven
Figure 3. FPT and FHPT when non-local countries $R_0$s increased by 20% or decreased by 20%. The upper panel (A) and the lower panel (B) illustrate the FPT and the FHPT respectively. Day one was taken to be March 11, 2009 (the time of the first global case onset). The medians are demonstrated as the dots in the interpolations; the corresponding lower and upper bounds of the 95% non-parametric confidence intervals are demonstrated as the lower cups and upper cups respectively.
months’ cumulative AR (Figure 4A). Similar to the baseline scenario, the travel restriction made greater impacts on slowing down the ARs increase with the use of antiviral and hospitalization (AH); a 99% rescaling of means of all transport controlled the final AR at about 20% in addition to the use of AH (Figure 4B). When the $R_0$s decreased by 20%, the travel restrictions performed better in slowing down the disease transmission. Even if only the air travel was either 90% or 99% restricted, the seven months’ cumulative ARs would have reduced about 15% compared to that of no intervention (Figure 4C). A 99% restriction of all means of transport would have halted the local spread i.e. cumulative ARs < 0.1% in seven months’ time whether or not the AH had been used (Figure 4C and 4D). However, the final cumulative ARs would not be affected by the changes of the $R_0$s from non-local countries.

**Variations of screening sensitivity at entry border points**

In the baseline scenarios, we set the screening sensitivity at entry border points as 30%; here, we assess the model’s output at extremely high (95%) and low (5%) screening sensitivities. According to Figure 5 and 6, the screening sensitivities at entry border points affected slightly on the times of cases arrival. Amongst most of the travel restriction strategies, a 95% screening sensitivity showed at most one to two weeks additional delay to the FHPTs compared to that of a 5% screening sensitivity (Figure 5).

The increase of the screening sensitivity at entry border points offered a moderate benefit on slowing down the growths of cumulative ARs. Showed in Figure 6A-D, a 95% screening sensitivity showed only half of five months’ cumulative ARs compared to that of a 5% screening sensitivity. The 95% screening sensitivity also decreased the seven months’ cumulative ARs by about 10% in most of the restriction strategies whether or not the AH had been imposed.
Figure 4. Median cumulative ARs on different time points when non-local countries’ $R_0$s increased by 20% or decreased by 20%. The upper panel (A and B) and the lower panel (C and D) show the cumulative ARs with the non-local countries’ $R_0$s increased by 20% and decreased by 20% respectively. The absences and the presences of the uses of the antiviral and hospitalization are illustrated in left-hand column (A and C) and right-hand column (B and D) respectively. The baseline scenario ($R_0 = 1.4$) was adopted.
Figure 5. FPT and FHPT when screening sensitivity increased to 95% or decreased to 5%. The upper panel (A) and the lower panel (B) illustrate the FPT and the FHPT respectively. Day one was taken to be March 11, 2009 (the time of the first global case onset). The medians are demonstrated as the dots in the interpolations; the corresponding lower and upper bounds of the 95% non-parametric confidence intervals are demonstrated as the lower cups and upper cups respectively.
Figure 6. Median cumulative ARs on different time points when screening sensitivity increased to 95% or decreased to 5%. The upper panel (A and B) and the lower panel (C and D) show the cumulative ARs with the screening sensitivities increased to 95% and decreased to 5% respectively. The absences and the presences of the uses of the antiviral and hospitalization are illustrated in left-hand column (A and C) and right-hand column (B and D) respectively. The baseline scenario ($R_0 = 1.4$) was adopted.
Variations of implementation date on travel restrictions

We tested the impact of delaying the imposition of travel restrictions to five and three months following the first global import. Showed in Figure 7A and 7B, imposing travel restrictions five months after the first global case arose would be too late obviously. Even if all means of transport had been 99% rescaled, the reduction in the cumulative AR was too small. However, it could still decrease the seven months’ cumulative AR by no more than 10% if the growth of the epidemic was slowed down by the use of AH. Showed in Figure 7C, imposing the travel restrictions three months after the first global case arose would be a little bit late; but fractional blockings on all means of transport worked well in deflecting the growth of the ARs. The 99% restriction would reduced the five months’ and seven months’ cumulative ARs more than half of that without intervention. With the use of AH, imposing the 99% restriction of all mean of transport was able to control the cumulative AR by no more than 2% in the first seven months; a 90% restriction could still maintain the average seven months’ cumulative AR about 6% to 7% (Figure 7D).

3 Sensitivity analysis

Time step of model

The simulation results were based on the stochastic models with a time step of $\Delta t = 1$ day. The simulations were repeated with $\Delta t = 0.5$ day. Figure 8 showed the results for comparison. According to the results, the incidence growth curves differed moderately compared with that of $\Delta t = 1$ day (main text, Figure 3); the daily ARs were less severe for scenarios with $\Delta t = 0.5$ day. However, there were only slight differences for the impacts of interventions on the baseline scenario between two kinds of time-step settings. For
Figure 7. Median cumulative ARs on different time points when implementation date of travel restrictions delayed for five months or three months. The upper panel (A and B) and the lower panel (C and D) show the cumulative ARs with the implementation dates on travel restrictions delayed for five months and three months respectively. The absences and the presences of the uses of the antiviral and hospitalization are illustrated in left-hand column (A and C) and right-hand column (B and D) respectively. The baseline scenario ($R_0 = 1.4$) was adopted.
example, a 99% restriction of all transport modes deferred the peak for about 12 weeks (Figure 8B) in both time-step settings. Models with either $\Delta t = 0.5$ day or $\Delta t = 1$ day drew similar conclusions in the study.

Figure 8. Daily incidences at the baseline scenario given $\Delta t = 0.5$ day. The absences and the presences of the uses of antiviral and hospitalization are illustrated in the left-hand column (A and C) and in the right-hand column (B and D), respectively. The upper panel (A and B) and the lower panel (C and D) illustrate the 90% and the 99% restriction rescaling, respectively. Day one was taken to be March 11, 2009 (the time of the first global case onset). The solid lines represent the average cases; the dotted lines represent the corresponding lower and upper bounds of the 95% non-parametric confidence intervals; AH = antiviral and hospitalization.

Multivariate sensitivity analysis

A multivariate sensitivity analysis which varied the following parameters with their prior distributions:

- Length of latent period (days) $\sim$ Uniform(range from 1 to 2)
• Sensitivity of the screening board for infectious subjects $\sim$ Uniform(range from 0.05 to 0.5)

• Length of infectious period reduction (days) by taking antivirals $\sim$ Uniform(range from 1 to 2)

• Length of infectious period reduction (days) by hospitalization $\sim$ Uniform(range from 1 to 2)

• Fraction of infectiousness reduction for antiviral treatment $\sim$ Uniform(range from 0.3 to 0.9)

was performed. Each random set of parameters was simulated before every realization.

Figures 9 and 10 showed the results. The incidence curves were moderately sensitive to the variations of parameters. Restrictions on a single mode of transport had less apparent impact due to moderate deviations. The range of peak times from imposing 99% restriction on all modes of transports was wider. However, the central tendency of the intervention effects were quite stable. The impacts of interventions on the baseline scenario did not differ much compared with the study main findings. For example, when a 99% restriction of all transports was imposed, the peak was averagely deferred to the ninth month and the eleventh month respectively in absences and presences of the uses of antiviral and hospitalization.

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Figure 9. Daily incidences in absences of the uses of antiviral and hospitalization for a multivariate sensitivity analysis. One hundred simulated curves were drawn in each figure: (A) No travel restrictions. (B) 90% air travel restrictions. (C) 90% sea travel restrictions. (D) 90% land travel restrictions. (E) 90% all travel restrictions. (F) 99% air travel restrictions. (G) 99% sea travel restrictions. (H) 99% land travel restrictions. (I) 99% all travel restrictions.
Figure 10. Daily incidences in presence of uses of antiviral and hospitalization for a multivariate sensitivity analysis. One hundred simulated curves were drawn in each figure: (A) No travel restrictions. (B) 90% air travel restrictions. (C) 90% sea travel restrictions. (D) 90% land travel restrictions. (E) 90% all travel restrictions. (F) 99% air travel restrictions. (G) 99% sea travel restrictions. (H) 99% land travel restrictions. (I) 99% all travel restrictions.
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