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Impact of quarantine on the 2003 SARS outbreak: A retrospective modeling study

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Abstract

During the 2003 Severe Acute Respiratory Syndrome (SARS) outbreak, traditional intervention measures such as quarantine and border control were found to be useful in containing the outbreak. We used laboratory verified SARS case data and the detailed quarantine data in Taiwan, where over 150,000 people were quarantined during the 2003 outbreak, to formulate a mathematical model which incorporates Level A quarantine (of potentially exposed contacts of suspected SARS patients) and Level B quarantine (of travelers arriving at borders from SARS affected areas) implemented in Taiwan during the outbreak. We obtain the average case fatality ratio and the daily quarantine rate for the Taiwan outbreak. Model simulations is utilized to show that Level A quarantine prevented approximately 461 additional SARS cases and 62 additional deaths, while the effect of Level B quarantine was comparatively minor, yielding only around 5% reduction of cases and deaths. The combined impact of the two levels of quarantine had reduced the case number and deaths by almost a half. The results demonstrate how modeling can be useful in qualitative evaluation of the impact of traditional intervention measures for newly emerging infectious diseases outbreak when there is inadequate information on the characteristics and clinical features of the new disease—measures which could become particularly important with the looming threat of global flu pandemic possibly caused by a novel mutating flu strain, including that of avian variety.

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1. Introduction

In order to contain the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003, the government in Taiwan implemented numerous measures of intervention and control (Kaydos-Daniels et al., 2004; Lee et al., 2003; Twu et al., 2003). Prominent among which is the Level A quarantine, implemented on March 17, for all possible contacts of suspected SARS cases which eventually reached a total of 55,632 individuals quarantined, and Level B

quarantine, implemented on April 28, of all travelers arriving at borders from affected areas which totaled 95,828 (see Table 1 in Hsieh et al., 2005). Other intervention measures implemented during the outbreak include temperature monitoring, SARS fever hotline, hand washing, restricted access to all medical facilities, fever screening at designated local hospitals, as well as mandatory face mask wearing while in hospitals, public transportation, and other enclosed public places, most of which were also implemented on April 28, the day after the first SARS fatality had occurred in Taiwan. Mathematical modeling has also pinpointed the turning point of SARS infections in Taiwan to April 28 (Hsieh et al., 2004).

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Table 1
Quarantine status of imported cases classified by before or after the implementation of Level B quarantine on April 28, 2003

	Officially confirmed cases			Laboratory confirmed cases		
	Number of cases	Onset after arrival	Quarantined (%)	Number of cases	Onset after arrival	Quarantined (%)
Before 4/28	16	9	1 (11.1)	14	8	0 (0)
After 4/28	3	1	0 (0)	2	1	1 (100)

It is generally acknowledged that intervention measures such as isolation of symptomatic cases and the quarantine of their traced contacts had been instrumental in controlling the past SARS outbreak (Chau and Yip, 2003; Diamond, 2003; Enserink, 2003; Ou et al., 2003; Pang et al., 2003). A recent modeling study (Fraser et al., 2004) suggests that SARS, along with smallpox, is easier to control using these simple public health measures than HIV and Influenza. However, due to the current lack of evidence regarding infectivity of SARS-CoV prior to onset, quarantine for SARS did not seem to directly prevent infections during the incubation period in the traditional sense. Indeed, it has been demonstrated that quarantine served as a screening process for SARS whereby previous quarantined persons who showed onset of symptoms can be more swiftly diagnosed and sufficiently isolated once onset of symptoms occurs (Hsieh et al., 2005).

In view of this rather indirect effect of quarantine in preventing infections, it is important to know precisely what role did an extensive quarantine measure such as the one implemented in Taiwan actually played in the eventual containment of the outbreak (Ho and Su, 2004). Moreover, the value of border screening and Level B quarantine in deterring travel by ill persons and building public confidence remains unquantified up to now (Bell, 2004). (Zhang et al., 2005) used a continuous-time compartmental model to study the impact of quarantine for SARS in China. In this article we propose to use discrete time model to ascertain retrospectively and qualitatively the impact of Level A and B quarantine measures in Taiwan by making use of the laboratory confirmed SARS case data in Taiwan.

2. Data

The quarantine data used in this work were obtained and cleaned from the original case data in Taiwan Center for Disease Control (TCDC) SARS databank (see Table 1 in Hsieh et al., 2005 for a summary). The SARS case data contains the clinical data from onset to discharge or death and the quarantine status of 480 confirmed SARS cases in Taiwan, including 346 SARS cases that were officially confirmed by TCDC and additional 134 laboratory confirmed SARS-CoV (Ab+) individuals who either had milder symptoms but were not clinically diagnosed as probable cases at the time of the outbreak, or probable cases who were previously ruled-out due to false negative PCR or Ab test results. These 134 cases were identified

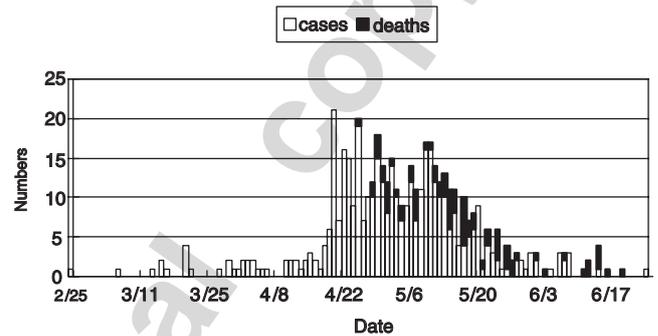


Fig. 1. Daily incidence by onset date and deaths of 461 SARS cases in Taiwan, 2/25–6/25, 2003. (Source: Taiwan CDC and Hsieh et al., 2005).

from a subsequent TCDC-sponsored large-scale seroepidemiological follow-up study to search for previously undiscovered SARS cases (Hsieh et al., 2005). All seropositive cases from this study were confirmed by two different serological tests to detect anti-SARS-CoV antibody once discrepancies occurred. The ongoing laboratory test results of these newly laboratory confirmed cases are updated as of November of 2004. The resulting percentages of all Level A and B quarantined persons who had been confirmed as SARS-CoV(+) cases are, respectively, 0.041% and 0.001%. The quarantine status of imported cases is given in Table 1.

Of the 346 officially confirmed cases in Taiwan, 336 have complete clinical records from onset to discharge or death. In addition, 125 of the 134 laboratory confirmed SARS-CoV(+) cases have complete clinical history from onset to discharge or death. We will use the case data of these 461 (336+125) confirmed cases with time of onsets between February 25 and June 25 for our modeling study (see Fig. 1). Note that one suicide case was also excluded from the case data used.

3. The model

We consider a Susceptible-Infective-Removal (SIR) model (flow diagram in Fig. 2) similar to the linear model in (Hsieh et al., 2004), but with additional compartments for Levels A and B quarantined persons (respective variables A_n and B_n), and for the previously quarantined infectives (J_n). Hospitalized cases (H_n) mean those who were diagnosed and hospitalized as a suspected SARS case, while the probable cases (P_n) are ones who has been classified as a probable SARS case according to the case

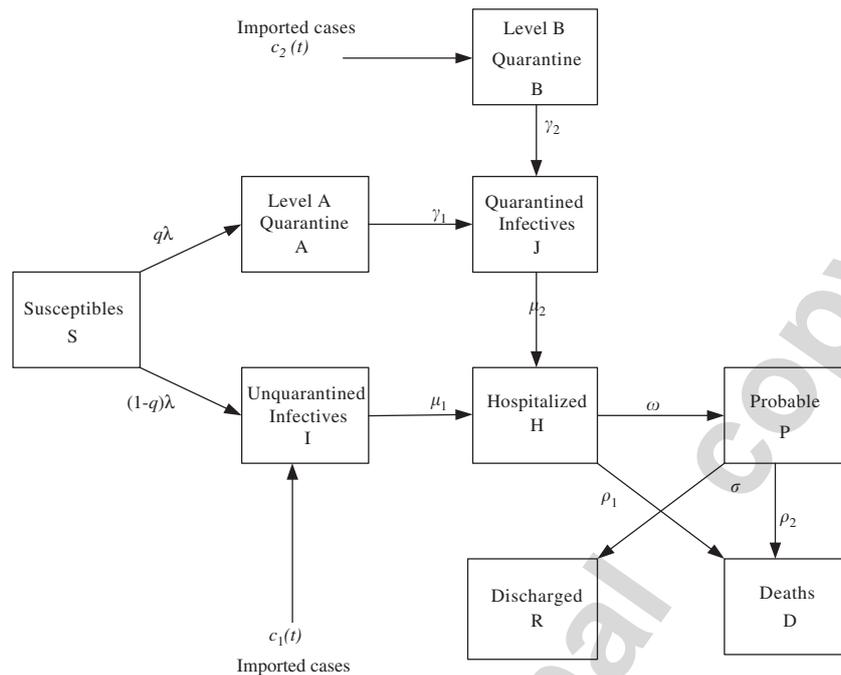


Fig. 2. SARS Model with Quarantine Measures (the time unit n for each compartment is omitted for brevity).

definition of (World Health Organization, 2003a). Note that the subscript n has been deleted in Fig. 2 for brevity.

The detailed model description is given as follows:

Model variables:

- S_n the number of susceptible individuals at time $t = n$
- A_n the number of Level A quarantined infected persons at time $t = n$
- B_n the number of Level B quarantined infected persons at time $t = n$
- I_n the number of infective (symptomatic) SARS cases at time $t = n$ not previously quarantined
- J_n the number of previously quarantined infective (symptomatic) SARS cases at time $t = n$
- H_n the number of hospitalized suspected cases at time $t = n$
- P_n the number of probable cases at time $t = n$
- R_n the cumulative number of discharged SARS cases at time $t = n$
- D_n the cumulative number of SARS deaths at time $t = n$
- $C_1(n)$ number of imported cases not quarantined when entering at time $t = n$
- $C_2(n)$ number of imported cases quarantined when entering at time $t = n$

Note that time unit is in days.

Assumption:

- (1) The number of imported susceptible persons and birth during the outbreak are small compared to the total susceptible population (S).

- (2) A person is moved out of susceptible class only after onset of symptoms and/or quarantine.
- (3) An infective person can infect others at either Infective (I and J) or hospitalized (H) stages.
- (4) A hospitalized case is removed either by reclassification to probable SARS case or death.
- (5) A probable case is removed either by discharge or death.

Parameters:

- q quarantined rate of infected persons
- $\gamma_j, j = 1, 2$ onset rate of Levels A and B quarantined persons, respectively
- $\mu_j, j = 1, 2$ hospitalization rate of unquarantined and previously quarantined infective cases, respectively
- ω rate of reclassification to probable cases
- σ discharge rate of probable SARS persons
- ρ_1 fatality rate of hospitalized SARS cases
- ρ_2 fatality rate of probable SARS cases
- λ_n incidence rate at time n
- β constant infection rate due to contact with an infective case (I)
- γ constant infection rate due to contact with a hospitalized case (H)
- η constant infection rate due to contact with a previous quarantined infective case (J)

The model equations with time unit in day then follows:

$$\begin{aligned}
 S_{n+1} &= S_n - \lambda_n, \\
 A_{n+1} &= A_n - \gamma_1 A_n + q\lambda_n, \\
 B_{n+1} &= B_n - \gamma_2 B_n + C_2(n),
 \end{aligned}$$

Table 2
Estimation results of the model parameters with the respective p -values using the 3SLS method

	Estimate	95%CI	p -value
Daily infection rate β	0.347	(0.3108–0.3837)	<.0001 ^a
Daily quarantine rate q	0.047	(0.0280–0.0667)	<.0001 ^b
Removal rate for Level A quarantine γ_1	0.176	(0.1330–0.2183)	<.0001
Removal rate for Level B quarantine γ_2	0.326	(0.2435–0.4094)	<.0001
Death rate for the hospitalized cases ρ_1	0.012	(0.0071–0.0163)	<.0001
Death rate for the probable cases ρ_2	0.009	(0.0056–0.0115)	<.0001
Discharge rate for the probable cases σ	0.053	(0.0465–0.0596)	<.0001

The weighted R -square for the estimation is $R^2 = 0.9983$.

^a p -value of $1 - \mu_1 + \beta(1 - q)$.

^b p -value of $q\beta$.

$$\begin{aligned} J_{n+1} &= J_n - \mu_2 J_n + \gamma_1 A_n + \gamma_2 B_n, \\ I_{n+1} &= I_n - \mu_1 I_n + (1 - q)\lambda_n + C_1(n), \\ H_{n+1} &= H_n - \omega H_n - \rho_1 H_n + \mu_1 I_n + \mu_2 J_n, \\ P_{n+1} &= P_n - \rho_2 P_n - \sigma P_n + \omega H_n, \\ D_{n+1} &= D_n + \rho_1 H_n + \rho_2 P_n, \\ R_{n+1} &= R_n + \sigma P_n, \end{aligned}$$

with

$$\lambda_n = \beta I_n + \gamma H_n + \eta J_n.$$

Note that we use a simple linear model instead of a nonlinear model with standard incidence or mass action since, in a small outbreak like SARS in 2003, the total susceptible population remained relatively unchanged. Also note that, theoretically, it is conceivable for q to be greater than 1 in a hypothetical scenario of highly efficient contact tracing and quarantine program. However, our aim is to study 2003 SARS outbreak retrospectively where we knew the quarantine was much less efficient in reality.

4. Estimation method

The parameter estimation for the model was carried out by fitting the time series of 361 confirmed SARS case data to the model using three-stage least-squares (3SLS) method, commonly used in econometrics for estimating multiple parameters of simultaneous equations (Pindyck and Rubinfeld, 1998). The detailed description of the 3SLS estimation procedure is given in the Appendix. To simplify the estimation, we will make use of previously published estimates of the model parameters for Taiwan SARS, whenever available. In Hsieh et al. (2005), the mean onset-to-diagnosis times for quarantined and unquarantined individuals were computed from the Taiwan SARS case data to be 1.20 days and 2.89 days, respectively, hence we obtain $\mu_2 = 1/1.2 = 0.833$ and $\mu_1 = 1/2.89 = 0.346$ for the respective removal rates of the quarantine and unquarantined infective. Moreover, also from the result in Hsieh et al. (2005), we can obtain $\omega = 1/7.55 = 0.132$ for the reclassification rate of the hospitalized persons.

5. Results

The estimates for the model parameters are given in Table 2 along with their respective p -values for the t -tests used to determine whether each parameter is significantly different from zero (statistical details relating to p -values obtained here are also given in the supplementary Information). The infections by the previously quarantined persons J_n and hospitalized patients H_n (γ and η) were determined by the model to be not significantly different from zero when compared with the infection during infective stages I_n and hence omitted from Table 2.

We proceed to describe the important epidemiological parameters and results which we can deduce from the estimation.

5.1. Average case fatality ratio for SARS

From the estimates we are able to obtain the average case fatality ratio for a SARS probable case conditional on death or recovery which is given by the simple formula:

$$\frac{\rho_2}{\rho_2 + \sigma} = \frac{0.009}{0.009 + 0.053} = 14.1\%,$$

where ρ_2 is the fatality of a probable case and δ is the discharge rate. That is, given that a probable case has only two possible outcomes of recovery or death, the chance of fatality is approximately one in nine, which is lower than the cumulative case fatality ratios (deaths/case number) reported in affected regions (Table 3, World Health Organization, 2003b).

5.2. Impact of Level A quarantine

The average daily quarantine rate for Level A quarantine is estimated to be $q = 0.047$ [95%CI: 0.0280–0.0677], which is the average rate at which potential candidates for quarantine (i.e. the asymptomatic exposed persons) on any particular day are in fact being quarantined. In other words, during this period one out of every 21 asymptomatic individuals who should be quarantined was indeed quarantined. Moreover, it is not significantly

Table 3

Theoretical impact of Level A quarantine on case number and fatality with various hypothetical quarantine rates q as compared with quarantine rate of $q = 0.047$ estimated from the model

	$q = 0.0$	$q = 0.025$	$q = 0.1$	$q = 0.6$	$q = 1.0$
Cases	+ 461 (81%)	+ 167 (29%)	–214 (–38%)	–477 (–84%)	–500 (–88%)
Deaths	+ 62 (63%)	+ 24 (24%)	–33 (–33%)	–80 (–81%)	–85 (–86%)

The percentage increase or reduction is given in parenthesis.
 + denotes additional cases, – denotes reduction in cases.

Table 4

Theoretical impact of Level B quarantine of imported cases under various hypothetical scenarios on the numbers of SARS cases and SARS fatality

	SARS cases	Deaths
If one un-quarantined imported case on May 2 had been quarantined	–12 (–2.2%)	–2 (–1.7%)
If all 17 un-quarantined imported cases had been quarantined	–280 (–49.2%)	–48 (–48.9%)
If one imported case quarantined on 3/28 had not been quarantined	+ 17 (3.0%)	+ 3 (3.1%)
If one imported case quarantined on 5/6 had not been quarantined	+ 12 (2.1%)	+ 2 (1.7%)
If both quarantined imported cases had not been quarantined	+ 29 (5.2%)	+ 5 (4.8%)
If no one was quarantined in Taiwan	+ 511 (90.0%)	+ 70 (70.8%)

The percentage increase or reduction from theoretical numbers of cases or death using the present model is given in parenthesis.
 + denotes additional cases, – denotes reduction in cases.

different from the overall quarantine rate of 0.05 (24 quarantined cases out of 480 total cases).

We can further make use of the results to explore the effectiveness of the quarantine implemented. For illustration, we let the quarantine rate for Level A quarantine q vary between 0 and 1, where $q = 0$ means no quarantine and $q = 1$ implies swift quarantine of locally exposed persons, i.e. everyone potentially exposed and should be quarantined on any particular day is being quarantined 24 h after exposure, on the average. We then compute the theoretical numbers of SARS cases and deaths using the model and designated value of q . Table 3 gives the resulting percentage of increase or reduction in the total numbers of SARS cases and deaths.

The result indicates that the Level A quarantine for SARS in Taiwan with 0.047 quarantine rate (which yields theoretical numbers of 569 cases and 99 deaths) had prevented approximately 461 cases (81%) and 62 deaths (63%), while a swift quarantine of $q = 1$, where everyone locally exposed and should be quarantined was quarantined on the first day, would have reduced both the case number and fatality by over 86%, or only 68 totally cases and 14 deaths. Note that in this theoretical scenario, the case number of 68 includes 35 imported cases, of which only one had been quarantined on arrival. Subsequently, local transmission by these unquarantined imported cases after onset contributes to the additional cases. Moreover, infective cases with minimum incubation time of 1 day (onset within 1 day of exposure) had been reported in China as well as Singapore (World Health Organization, 2003b), further leading to the possibility of local transmission by these locally infected cases before quarantine. Only

$q \rightarrow \infty$ implies quarantine for every locally exposed individual immediately after exposure, which would prevent all cases except those 35 imported cases mentioned above and their first level infecteds of those unquarantined on arrival.

5.3. Impact of Level B quarantine

We proceed in similar fashion with regard to Level B quarantine by computing the theoretical increase in the numbers of SARS cases and deaths if the single quarantined imported case had not been quarantined, as well the reductions if the unquarantined imported cases had been quarantined. Table 4 gives the results of this theoretical study.

First we study the impact of one imported case who arrived from China on May 2 via sea but was not quarantined even though, starting on April 28, full-scale quarantine of all border arrivals from China were required to be home quarantined for 14 days. Failure to quarantine this individual, who had onset of symptoms on May 7 and was diagnosed and hospitalized the next day, resulted in approximately 12 cases and 2 death (row 1). Moreover, if Level B quarantine had been implemented from the beginning of the outbreak and all imported cases were successfully quarantined at the border, it would result in 49% reduction in cases and in SARS fatality (row 2).

There were only two successful quarantined (Level B) imported cases, both arriving from China. The first was quarantined on arrival on March 28, developed symptoms on April 1 and was diagnosed as suspected case and

quarantined on April 2. Our simulation shows that if this successful quarantine of this imported case had not occurred, it would result in approximately 17 cases and three deaths (row 3). The second quarantined imported case was quarantined on arrival on May 6, had onset of symptoms on May 8 and was diagnosed and hospitalized immediately. Quarantine of this case prevented approximately 12 additional cases and two death (row 4). Quarantine of the earlier case is only slightly more impactful. The combined effect of these two quarantined cases prevented 29 cases and five deaths (row 5). The combined effect of all quarantines reduced the case number and fatality almost by half (last row).

6. Conclusions and discussion

- (1) In a fast spreading infectious disease with unknown or uncertain knowledge of the etiological agent, the effectiveness and efficiency of control efforts are of the highest priority. The quarantine rate q gives a measure of the *efficiency*, or the *speed*, at which a potential Level A quarantine case is actually being quarantined. Thus quarantine rate of 0.047 estimated over the time period 2/25–6/25 indicates that, on a daily basis, only one out of every 21 exposed persons who should be quarantined was actually quarantined. This reflects the need for more efficient real-time contact tracing during the outbreak in order to seek out potential infected persons for quarantine, observation, and swift diagnosis when onset of symptoms occurs. One should note, however, that the data used includes many mild cases that were not clinically diagnosed and hence their exposed contacts were not traceable. This would result in a significantly lower quarantine rate than the one computed from using clinically diagnosed SARS cases only. Hence the efficiency of contact tracing and quarantine is also dependent on correct diagnosis of symptomatic infective individuals, which could be severely lacking in the early stages of a newly emerging disease such as witnessed during the past SARS outbreak.
- (2) The contribution to infections by the previously quarantined (J_n) and hospitalized (H_n) persons appeared to be insignificant when compared with the infection by the infectives in I_n . This does not mean infections by J_n and H_n had not occurred, merely that their effects were relatively insignificant. In fact, 80% of the officially confirmed SARS cases in Taiwan were acquired in hospitals (Ho and Su, 2004), but the many of them occurred *prior* to the patients' hospitalization as a suspected SARS case, while they were in outpatient clinics, observation rooms, and emergency rooms, sometimes for other illness, where the patients often stayed for hours and sometimes for days before being moved (Jiang et al., 2003a, b). Many of those infected were also in the hospital as healthcare workers, hospital staff, and visitors. This also indicates that, in term of intervention, rapid initial detection is much more important than subsequent classification of probable cases.
- (3) By comparison, a perfect Level A quarantine (which aimed to quarantine all asymptomatic cases as soon as they were potentially exposed) results in more drastic reduction of cases than a perfect Level B quarantine. However, it is intuitive that if all imported cases were effectively isolated, there would be no local outbreak. Indeed, from our result the timeliness of Level B quarantine is important, as indicated by the difference in the reduction of cases by the two quarantined imported cases. Given the controversial nature of full-scaled quarantine of international travelers, appropriate mathematical modeling is required to provide evidence-based criterion for public health authority to determine its swift implementation. The difficulty and scope involved in a successful quarantine, as quantified in Tables 3 and 4, gives strong indication that quarantine must be combined with other intervention measures for successful and swift containment of an outbreak. The results also corroborate with previous studies of intervention measures for SARS outbreak where hospital-wide case isolation is found to be more important than quarantine (see e.g., Day et al., 2006; Gumel et al., 2004; Lloyd-Smith et al., 2003; Webb et al., 2004).
- (4) The simulation results in Tables 3 and 4 highlight the effect an efficient quarantine measure could have on significantly reducing the magnitude of the outbreak. We emphasize, however, that the numbers of reduction and increase in cases and deaths shown in Tables 3 and 4 are not to be taken literally, but to be consider qualitatively as a measure of the magnitude of the effect brought on by the various hypothetical scenarios for the purpose of comparing different control measures. However, there is ample evidence that superspreading events had played a significant role in the 2003 outbreaks (Li et al., 2004; Riley et al., 2003) which was not singled out in our model.
- (5) Finally, the effect of public response to outbreak and behavior change to prevent infection is most difficult to quantify. Question remains as to how one can pinpoint the degree of effectiveness or the relative importance of different measures implemented. One may never know for certain how important temperature monitoring or hand washing had been to the containment of the outbreak, or what role, if any, did mandatory face mask wearing in public transportation systems play, or whether the decrease in infection rate is merely due to the psychological effect of outbreak and the subsequent behavior change by the general population to simply try to stay home and avoid contacts—especially since multiple prevention measures were co-operating at the same time in blocking all possible channels of the transmission of SARS-CoV. One thing is certain, all of these intervention measures and the subsequent in-

dividual behavior changes combined to prevent the past SARS epidemic from being more catastrophic than it was, and will be our best defense when the next emerging infectious disease approaches.

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Appendix. Parameter estimation procedure

A1. Parameter estimation

To estimate the model parameters, we treat a linear system of equations a multi-equation simulation model, which allows us to account for the interrelationship within a set of variables, namely, A_n , B_n , J_n , I_n , H_n , P_n , and D_n , which are called endogenous variables in econometrics (Pindyck and Rubinfeld, 1998). Two-stage least-squares (2SLS) and three-stage least squares (3SLS) can both provide a very useful estimation procedure for simultaneous equation. However, 2SLS is inefficient when the system of equations contains lagged dependent variables, which account for adjustments that take place over time. We can achieve a gain in efficiency by applying 3SLS. It involves applying generalized least-squares estimation to a system of equations, each of which has first been estimated using 2SLS. The 3SLS procedure, also used for the parameter estimation in the simpler linear model in (Hsieh et al., 2004), yields more efficient parameter estimates than does 2SLS because it takes into account the cross-equation correlation and hence is utilized here for parameter estimation. Furthermore, we make use of the 3SLS subroutine in SAS package to estimate the model parameters.

A2. p -value

We add an error term in each equation when we employ 3SLS to estimate the unknown parameters. Moreover, to perform hypothesis tests for our model, we assume that the error terms follow a Gaussian distribution in order to test whether each parameter is significantly different from zero. We would like to test for $H_0: \beta = 0$ (null hypotheses) versus $H_1: \beta \neq 0$ (alternative hypotheses). Large value of t -statistic

or small value of p -value leads to conclude that $H_1: \beta \neq 0$. The p -value is less than the specified level of significant $\alpha = 0.05$, we could conclude H_x directly. The last column of Tables 2 and 3 give the p -values for the estimations, indicating that the data are not consistent with $\beta = 0$. Note that the p -value is sometimes called the observed level of significance, with which one can conduct a test at any desired level of significance α by comparing the p -value with the specified level α .

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