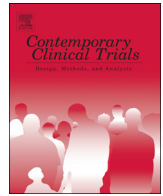




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# The effect of preventing subclinical transmission on the containment of COVID-19: Mathematical modeling and experience in Taiwan

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## ABSTRACT

The control strategies preventing subclinical transmission differed among countries. A stochastic transmission model was used to assess the potential effectiveness of control strategies at controlling the COVID-19 outbreak. Three strategies included lack of prevention of subclinical transmission (Strategy A), partial prevention using testing with different accuracy (Strategy B) and complete prevention by isolating all at-risk people (Strategy C, Taiwan policy). The high probability of containing COVID-19 in Strategy C is observed in different scenario, had varied in the number of initial cases (5, 20, and 40), the reproduction number (1.5, 2, 2.5, and 3.5), the proportion of at-risk people being investigated (40%, 60%, 80%, to 90%), the delay from symptom onset to isolation (long and short), and the proportion of transmission that occurred before symptom onset (< 1%, 15%, and 30%). Strategy C achieved probability of 80% under advantageous scenario, such as low number of initial cases and high coverage of epidemiological investigation but Strategy B and C rarely achieved that of 60%. Considering the unsatisfactory accuracy of current testing and insufficient resources, isolation of all at-risk people, as adopted in Taiwan, could be an effective alternative.

## 1. Introduction

The high infectiousness of SARS-CoV-2 with its ability to transmit during incubation period or by subclinical cases results in global pandemic. The virus has caused 1,923,937 infections and 119,618 deaths worldwide (as of April 13) [1]. A previous modeling study [2] showed that a combination of contact tracing and cases isolation is beneficial to the containment of COVID-19. However, the presence of subclinical transmission hampers greatly the effect of such control measures because those unidentified cases might become the source of community outbreaks. A common approach of testing on at-risk people could only identify part of the subclinical cases. It is therefore extremely difficult

to contain the spread of SARS-CoV-2.

Around eighty miles from the coast of mainland China, Taiwan had been predicted to be the “second highest import risk” of COVID-19 in the world [3]. As the COVID-19 pandemic spreads around the world, Taiwan has only 393 confirmed cases with majority of them being imported cases, which ranks below 97 countries and regions (as of April 13) (Fig. 1) [4,5]. The lack of large-scale outbreaks could be attributable to immediate quarantine upon identification of all at-risk people and follow-up, which mainly prevents the subclinical spread (Fig. 2) [6]. However, these measures may not be feasible in all countries. Due to a variety of control strategies worldwide, we used a stochastic transmission model, initially proposed by Hellewell et al. [2], to assess

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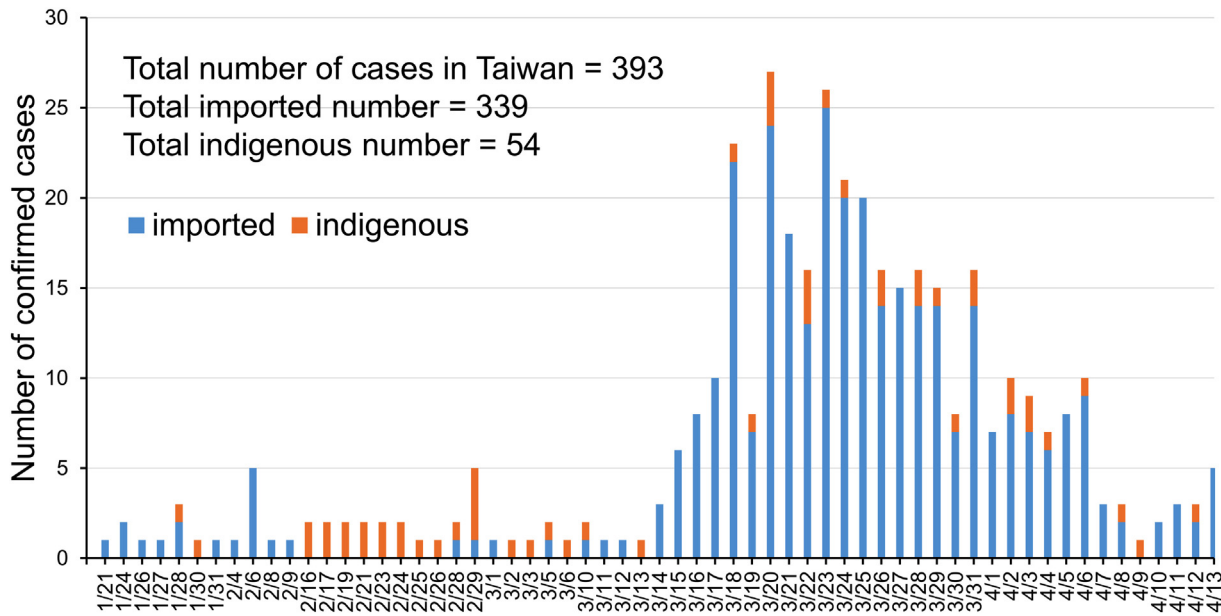


Fig. 1. COVID-19 cases in Taiwan by April 13, 2020.

the potential effectiveness of these control strategies at controlling the COVID-19 outbreak.

2. Material and methods

A stochastic transmission model proposed by Hellewell et al. [2], was established to assess the feasibility of contact tracing and case isolation to control outbreaks of COVID-19. With input parameters such as, percentage of subclinical cases, epidemiological investigation, isolation effectiveness, incubation period, the number of initial cases, the number of secondary infections generated by each new infection, and serial interval, this mathematical model could evaluate the probability of outbreak control on COVID-19 via simulations. Under the same model assumptions but incorporating COVID-19 cases in Taiwan and different control strategies, the stochastic transmission model, introduced by Hellewell et al. [2], could be used to simulate the probability of successful containment.

For each case of COVID-19, we assumed that the incubation period of each case was drawn from a Weibull distribution. That is, assumed that a random variable  $X$  represents the incubation period and follows a Weibull distribution with a shape parameter  $k$  and a scale parameter  $\lambda$ , where the corresponding probability density function is

$$f(x) = \begin{cases} \frac{k}{\lambda} \left(\frac{x}{\lambda}\right)^{k-1} e^{-\left(\frac{x}{\lambda}\right)^k} & x \geq 0 \\ 0 & x < 0 \end{cases}$$

The mean and the variance are

$$\lambda\Gamma(1 + 1/k) \text{ and } \lambda^2(\Gamma(1 + 2/k) - \Gamma(1 + 1/k)^2),$$

respectively, where  $\Gamma$  is the gamma function. The parameters  $k$  and  $\lambda$  were determined once mean and variance have been given (please see the incubation period in Table 1). Similarly, we assumed that the delay between symptom onset and isolation for each case was drawn from a Weibull distribution.

Let  $Y$  be the number of potential secondary cases produced by each primary case. Assume that  $Y$  follows a negative binomial distribution with a mean equal to a reproduction number  $R$ . Each potential new infection was assigned a time of infection drawn from the serial interval distribution. The corresponding serial interval for each case was drawn from a skew normal distribution. More specifically, let  $S$  be a random variable to represent a time of infection for each new case and  $S$  follows

a skew normal distribution [7]. Then the corresponding probability density function is

$$f(s) = \frac{2}{\omega} \phi\left(\frac{s - \xi}{\omega}\right) \Phi\left(\alpha \left(\frac{s - \xi}{\omega}\right)\right), s \geq 0$$

where  $\phi$  and  $\Phi$  are the standard normal probability density function and the corresponding cumulative distribution function, respectively. The location parameter  $\xi$  of this skew normal distribution was set to drawn from the incubation period for the case and the scale parameter  $\omega$  is 2. The value of shape parameter  $\alpha$  is used to control a set proportion of serial interval which were shorter than the incubation period (meaning that a set proportion of transmission happened before symptom onset). For example, if  $\alpha = 30$ , then the proportion of transmission before symptoms is

$$P(S - \xi < 0 \mid \omega = 2, \alpha = 30) = 0.0106$$

Similarly, the proportions of transmission before symptoms are 0.1508 and 0.3055 for given  $\alpha = 1.95$  and 0.7, respectively. Parameter values for the model were displayed in Table 1.

Note that secondary cases were only created if the infected person had not been isolated by the time of infection. In addition, we assume that each case had an independent probability of being subclinical. For example, if the percentage of subclinical infection  $p = 40\%$ , then each case had a 40% chance of being subclinical. New symptomatic secondary cases were isolated on the basis of symptoms, which prevented further transmission. In contrast, secondary subclinical cases were identified and/or isolated depending on control strategies.

The control strategies in different countries could be roughly divided into (A) epidemiological investigation and isolation of symptomatic cases, (B) Strategy A plus testing of all subclinical at-risk people, isolation positive cases and (C) Strategy A plus isolation of at-risk people. In this model, we assumed these strategies differed mainly in the ability to prevent subclinical transmission. Under the first strategy, subclinical cases freely spread. Under the second strategy, we assumed the testing identified and isolated 40%, 60%, or 80% of subclinical cases, which prevented subclinical transmission. Isolation of all at-risk people was assumed to completely prevent subclinical spread since the subclinical cases were isolated like symptomatic ones.

We considered the effect of the three strategies in different scenarios that varied in the number of initial cases (5, 20, and 40), the reproduction number ( $R$ ; 1.5, 2, 2.5, and 3.5), the proportion of at-risk

Intervention	14-day home isolation	14-day home quarantine	14-day self-health management
Criteria	Contact with confirmed cases	Travel to endemic area	Suspected of contracting COVID-19 but tested negative
Responsible authorities	Local health authorities	Local civil affairs bureau or borough chief	Self-management
Restrictions	Stay at home or designated location and not go out		Avoid public places, wear a surgical mask, practice common hygiene
Health check	Twice daily by public health system	Once or twice daily by civic system	Take temperature twice daily
If symptoms appear	Health authorities arrange immediate medical attention	Health authorities arrange testing	Report to epidemic monitoring hotline
Penalties	Mandatory medical isolation or other penalties under Communicable Disease Control Act		No

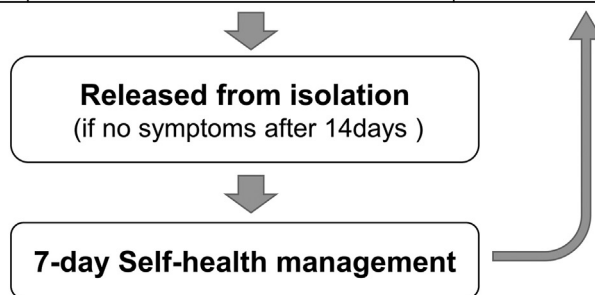


Fig. 2. Measures for following up on persons at risk of contracting COVID-19 in Taiwan.

Table 1  
Parameter values for the model.

	Value	Reference
<b>Sampled</b>		
Delay from onset to isolation (short and long)	2.9 days (3.0) and 7.36 days (5.58)	[8] and Cases in Taiwan
Incubation period	5.8 days (2.6)	[9]
Serial interval	Incubation period (2)	Assumed
<b>Fixed</b>		
Initial cases	5, 20, 40	[10]
Proportion of at-risk people being investigated	40%, 60%, 80%, 90%	Tested
Reproduction number (R)	1.5, 2, 2.5, 3.5	Tested
R after isolation	0	Assumed
Being isolated once identified	100%	Assumed
Isolation effectiveness	100%	Assumed
Percentage of subclinical cases	40%	[11]
Percentage of subclinical transmission prevented	0% (Strategy A), 40% (B1), 60% (B2), 80% (B3), 100% (C)	Tested
Pre-symptom transmission	1%, 15%, 30%	Tested

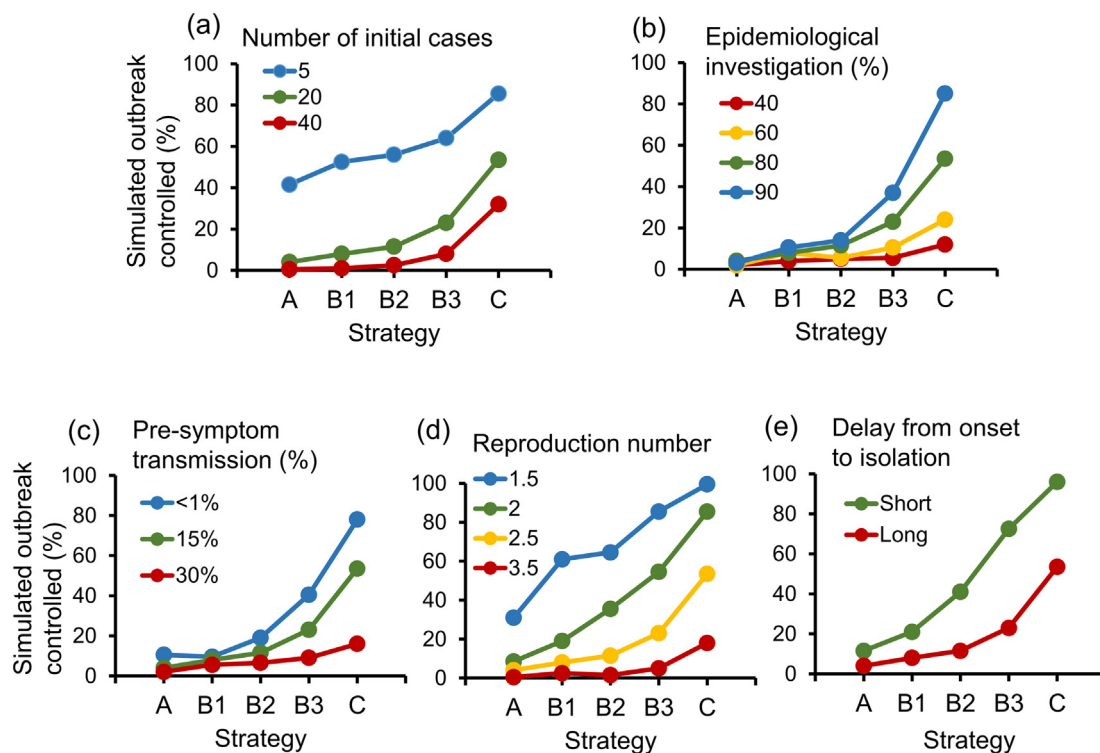
Data are mean (SD) or Median (95% CIs), n or %.

people being investigated (40%, 60%, 80%, and 90%), the delay from symptom onset to isolation (long and short), and the proportion of transmission that occurred before symptom onset (< 1%, 15%, and 30%). We assumed isolation prevented all further transmission in the model. Outbreak control was defined as no new infected cases between 12 and 16 weeks; outbreaks that reached 5000 cumulative cases were assumed to be too large to control within 12–16 weeks.

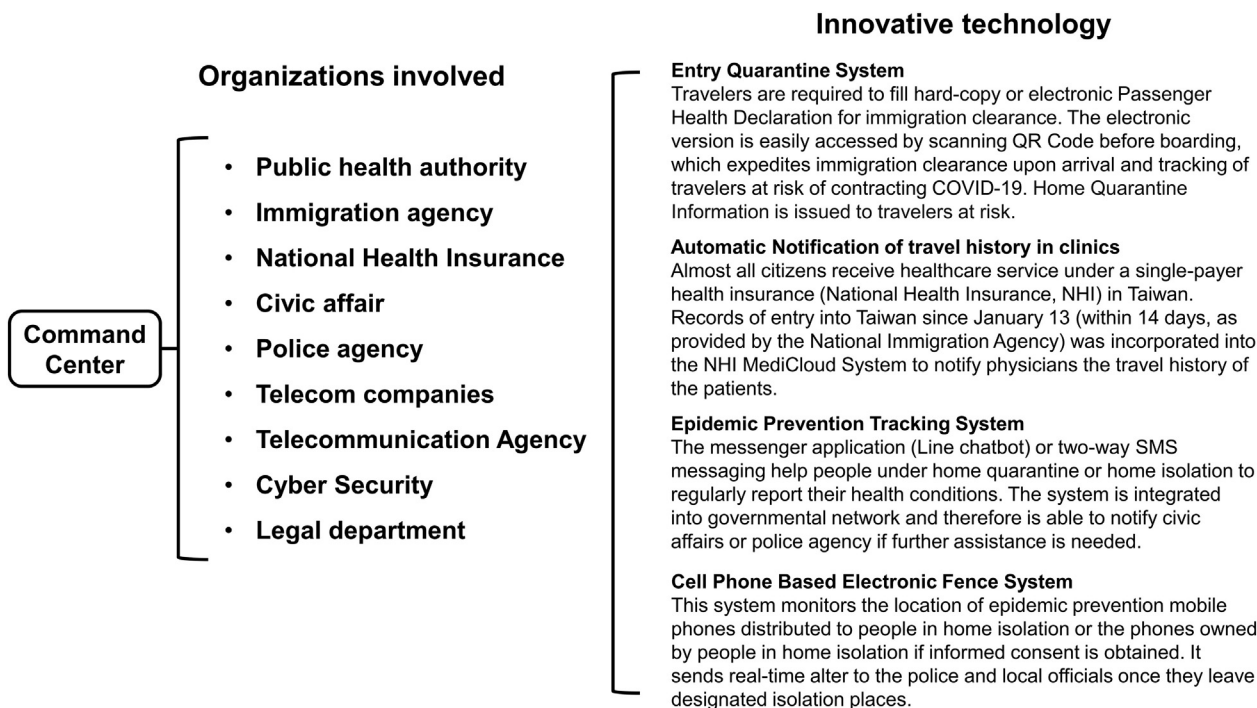
### 3. Results and discussion

Fig. 3 displays the probability of simulated outbreaks controlled under different strategies. The probability of containment of infectious diseases is highly contingent on the percentage of subclinical cases not being identified and/or isolated. In five transmission scenarios, isolation of all at-risk people (Strategy C) greatly increased chance to control outbreak. The probability of outbreaks controlled in Strategy A and B hardly achieved 60%. In contrast, the probability of success under Strategy C achieved 80% under advantageous condition, which may be present in Taiwan.

In this model, we assumed that quarantine of all at-risk people is beneficial, comparing with other strategies, only because of prevention of subclinical transmission. The quarantine of at-risk people may also



**Fig. 3.** The effect of control strategies on the probability of simulated outbreaks controlled under different transmission scenarios. X-axis represents three strategies that differed in the ability to prevent subclinical transmission. We assumed that 40% of total cases were subclinical. Strategy A prevented no subclinical transmission; Strategy B prevented 40% (B1), 60% (B2), or 80% (B3) of subclinical transmission by isolating subclinical cases after testing. Strategy C prevented all subclinical transmission by isolating of all at-risk people. The number of initial cases was 20 for (b)–(e). Assume 15% of transmission before onset for (a), (b), (d), (e). Assume reproduction number  $R = 2.5$  for (a)–(c), (e).



**Fig. 4.** Innovative technology that facilitate case identification, epidemiological investigation, and quarantine in Taiwan.

minimize the delay from symptom onset to isolation and reduce the chance of pre-symptom transmission, both of which were shown to increase the chance of containing outbreaks (Fig. 3(c) and (e)). The low initial case and high coverage of epidemiological investigation in

Taiwan also increase the chance of outbreaks controlled (Fig. 3(a) and (b)). Taiwan Central Epidemic Command Center issued travel restriction to various regions daily based on the epidemic data. The number of daily confirmed case in Taiwan has seldom passed 25, with average of

5. The high percentage (83%) of indigenous confirmed cases being traced to known sources indicates good coverage of epidemiological investigations in Taiwan. The reproduction number in Taiwan is assumed to be lower than 2.5 (Fig. 3(d)) because the community response to COVID-19 in Taiwan is swift and drastic due to the grave consequences of SARS in 2003. The responses include nationwide and social media campaign on infection control measures, social distancing, regular cleaning and disinfection and temperature monitoring in public transportation and public places, flexible work arrangement, avoidance of mass gathering, and streamline of religious rituals or events. All factors attributed to the lack of community outbreaks in Taiwan, as shown in the statistical model (Fig. 3).

Taiwan government dedicates to ensure the adherence of quarantine of all at-risk people, which is time- and labor-consuming. The cumulative number of quarantined people has reached 110,000 by April 6 [12]. Innovative technology has been introduced to facilitate the process and share the burden of public health officers. These integrated systems include Entry Quarantine System [13], automatic notification of travel history from National Health Insurance, Epidemic Prevention Tracking System, and Cell Phone Based Electronic Fence System (Fig. 4). They provide active surveillance on symptoms of all at-risk people and real time notification, which simplify epidemiological investigation, increase their awareness, and improve quarantine adherence. Taiwan government also provides incentives to increase the adherence of quarantine, including protection of labor right, compensation for those under quarantine or their caregivers, and provision of daily necessities.

#### 4. Conclusions

Our model demonstrated the importance of early identification and/or isolation of subclinical cases in containing the transmission. Our results suggest that a highly accurate testing, which can improve the detection of subclinical cases, is important to contain transmission. Considering the unsatisfactory accuracy of testing and insufficient resources, isolation of all at-risk people, as adopted in Taiwan, could be an effective alternative.

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