



Economic evaluations of inactivated COVID-19 vaccines in six Western Pacific and South East Asian countries and regions: A modeling study

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ABSTRACT

Objective: The present study aimed to document the economic profiles of inactivated COVID-19 vaccines in Hong Kong SAR, Indonesia, mainland China, Philippines, Singapore, and Thailand, the evidence on which is currently absent.

Methods: Decision tree models were developed to assess the cost-effectiveness of two doses of inactivated COVID-19 vaccines at a population vaccination rate of 50% in the base case, which was an estimate of feasible vaccination coverage according to previous studies. Epidemiological, mortality, cost, and health state utility information were sourced from the literature. Vaccine efficacy against COVID-19 cases by severity were estimated using meta-analyses of publicly accessible phase 3 trial results of inactivated vaccines. The health outcomes were quantified as quality-adjusted life years (QALYs) and compared across the vaccination and no vaccination strategies. In scenario analyses, incidence and vaccination rates were changed semi-continuously over spectrums, the results of which were presented as contour lines informing the efficiency frontiers of vaccination strategies. One-way and probabilistic sensitivity analyses were also conducted.

Results: The vaccination strategy was dominant in all jurisdictions in the base case by producing 105.18, 98.15, 99.70, 60.48, 112.00, and 103.47 QALYs while saving US\$40.26 million, US\$5.26 million, US\$7.60 million, US\$5.91 million, US\$21.33 million, and US\$7.18 million in Hong Kong SAR, Indonesia, mainland China, Philippines, Singapore, and Thailand per every 100,000 vaccinated individuals, respectively. Results were robust in alternative model specifications.

Conclusions: Inactivated COVID-19 vaccines may be cost-saving options in Hong Kong SAR, Indonesia, mainland China, Philippines, Singapore, and Thailand. Mass vaccination programs using inactivated COVID-19 vaccines should be considered in these jurisdictions.

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1. Introduction

As of the 1st week of Oct 2021, over 235 million cumulative COVID-19 cases have been reported globally (World Health Organization, 2021a). With the pandemic persisting into another year, many countries and regions sweated to roll out vaccination plans, which were made possible by encouraging outputs of unprecedented commitments to developing vaccines against SARS-Cov-2. In fact, COVID vaccination is considered to have a pivotal role in many pandemic exit strategies that are being considered (Bubar et al., 2021; Griffin et al., 2021; The Lancet Infectious). By Oct 8, 2021, twenty-four vaccines have seen full or conditional approvals in at least one country, followed by six competitors that have been authorized for emergency or limited use (McGill COVID19 vaccine tracker team, 2021). These vaccines were developed using different technologies including genetic vaccines, viral vector vaccines, and inactivated vaccines (McGill COVID19 vaccine tracker team, 2021; Zimmer et al., 2021). Whereas other technologies such as protein-based vaccinology is also being employed, the corresponding products have not yet taken the leading positions in clinical development. Due to the different biological nature, the vaccines currently available are likely associated with unequal efficacy, delivery and storage requirement, manufacturing challenges, prices, and perhaps safety.

Among these alternatives, inactivated vaccines are arguably the least demanding to deploy (Mallapaty, 2021). For example, inactivated vaccines can be shipped and shelved for over 3 years at regular fridge temperatures of 2–8 °C (Mallapaty, 2021; Xinhua. Inside China's Co, 2021). By contrast, most of the mRNA and adenovirus-vectored vaccines need to be shipped, delivered, or stored at a temperature of –20 °C and lower, which is a nontrivial hindrance to the distribution of vaccines in many low- and middle-income countries (LMICs) (Holm and Poland, 2021). Whereas one of the adenovirus-vectored vaccines, AZD1222, can also accommodate to refrigerators of 2–8 °C, the corresponding shelf life is only 1/5 of that of the inactivated vaccines (Holm and Poland, 2021; Zimmer et al., 2021). The lack of robust ultracold chain infrastructures may cause disproportionate damage to vaccine accessibility in LMICs, exacerbating healthcare inequality (Rostad and Anderson, 2021). As such, numerous LMICs have started immunizing the population with inactivated vaccines (Craven, 2021). In fact, several high-income countries and regions such as Hong Kong Special Administrative Region (SAR) and Singapore have also secured access to inactivated vaccines (Baraniuk, 2021; Yong, 2021).

Economic evaluations help to inform complex public health decision-making by weighing the costs against the benefits (Mauskopf et al., 2018). However, there is a dearth of information on the economic profiles of inactivated vaccines in the jurisdictions that have authorized their use. Whereas it is tempting to rely on intuition to favor the use of inactivated vaccines, formal cost-effectiveness analyses are necessary to shed light on the value of these products compared with no vaccination. As such, we aimed to conduct economic evaluations of immunizing the population using inactivated vaccines in Hong Kong SAR, Indonesia, mainland China, Philippines, Singapore, and Thailand. Inactivated vaccines that have been fully approved or authorized in two or more jurisdictions in the target countries and regions were eligible for analysis.

2. Methods

2.1. Setting

We developed a decision tree model to evaluate the incremental cost-effectiveness ratio (ICER) of immunizing with inactivated COVID-19 vaccines compared with no vaccination from the societal perspective in six countries and regions. Specifically, a Western Pacific and South East Asian country or region was eligible for inclusion if it has been delivered of either HB02 (one of the inactivated vaccines included in the current analysis) or CoronaVac (the other inactivated vaccine included in the current analysis) by Feb 2021. The analysis was conducted separately for each jurisdiction. To enable each analysis, a hypothetical cohort of 100,000 individuals from the general population in each jurisdiction were modeled using a one-year simulation time frame, in which mortality-related quality-adjusted life year (QALY) and productivity loss were also incorporated. The analyses pertain to the policy question of whether it is cost-effective to use inactivated COVID-19 vaccines for mass immunization programs at the current acquisition prices compared with no vaccination in a relatively natural state of epidemic intensity. A base-case scenario of disease incidence and vaccination rates was used for all countries, with various combinations of incidence and vaccination rates explored as robustness checks.

2.2. Intervention and efficacy

The analysis compared two doses of inactivated COVID vaccine with no vaccination by pooling the efficacy profiles of several inactivated vaccines. As of Oct 8, 2021, eight inactivated vaccines were approved or authorized for limited use in at least one country or region globally, two of which were eligible for the present analysis because they were accessible in two or more target jurisdictions of the present analysis (McGill COVID19 vaccine tracker team, 2021). Namely, the two vaccines are HB02 (also known as BBIBP-CorV) and CoronaVac, both of which are two-dose regimens injected 3–8 weeks apart (Xia et al., 2021; Zhang et al., 2021). According to data readings released by government authorities in different countries where phase 3 trials of the two vaccines were conducted, the vaccine efficacy (VE) against symptomatic COVID-19 cases of the former ranged between 78.1% and 86% whereas that of the latter had mixed reports spanning from 50.4% to 91.25% (Mallapaty, 2021; Wee and Qin, 2021; E: Ministry of Health a, 2020; Al Kaabi et al., 2021; Palacios et al., 2021; World Health Organization, 2021b). In the meantime, both vaccines were reported to be 100% efficacious against severe cases requiring hospitalizations (Mallapaty,

2021; Wee and Qin, 2021; E: Ministry of Health a, 2020). In addition to the two inactivated vaccines mentioned above, the manufacturer of HB02 also produces a third type of inactivated vaccine, which is known as WIV04 (Al Kaabi et al., 2021). In fact, its efficacy was tested in the same pivotal phase III trial (NCT04510207) as HB02. To obtain the efficacy estimates of inactivated vaccines for the base case scenario, a random-effect meta-analysis was conducted in this study to pool the information from four clinical trials covering HB02, WIV04, and CoronaVac (Al Kaabi et al., 2021; Palacios et al., 2021; World Health Organization, 2021b). In this meta-analysis, the arms of HB02 and WIV04 in the NCT04510207 clinical trial were combined as one arm. The outputs of the meta-analysis were the VE estimates against symptomatic infections. It was unnecessary to meta-analyze the VE against severe cases because the reported VE was 100% for all types of vaccines across the four trials. In addition, the trials of CoronaVac only reported VE against symptomatic but not asymptomatic cases. Therefore, the overall VE against any infection was based solely on the NCT04510207 clinical trial by conducting a logistic regression in which the HB02 and WIV04 arms were pooled as one arm. According to the results of the meta-analysis and the logistic regression, the VE of inactivated vaccines against symptomatic cases and any infections were 69.9% (95% CI: 47.6%–82.7%) and 68.7% (58.1%–76.7%), respectively (Table S1 and Fig. S1). It was assumed that the first dose allowed half of the maximum efficacy during the 4-week interval. Finally, the VE against mild and moderate cases was assumed to be the same as that for symptomatic infections since severe cases accounted for a minuscule proportion of all symptomatic cases in the trials (Al Kaabi et al., 2021; Palacios et al., 2021). In scenario analyses that are detailed in a later section, the profile of each type of inactivated vaccine was used. The efficacy estimates of any infections, symptomatic infections, mild and moderate cases, and severe cases were applied to the corresponding chance nodes in the decision tree.

It is unclear to what extent the populations in different countries and regions will be vaccinated, nor are the landscapes exactly unambiguous at the current stage. The scope needs to be defined by the target population per region-specific policies, capacity of vaccine manufacturing and procuring, and willingness to accept vaccination. Things taken together, a study estimated that about 3.7 billion people are to be vaccinated, which was about 50% of the world population (Wang et al., 2020a). Accordingly, the vaccination rate was set at 50% in the base case.

2.3. Model structure

Decision tree models are frequently employed for diseases in which the duration is short and recurrent events are rare (Gray et al., 2010). The decision tree model in the present study started with a group of uninfected general population and evaluated the one-year life course of the hypothetical cohort under the vaccination and no vaccination strategies in parallel. The model structure is schematized in Fig. 1.

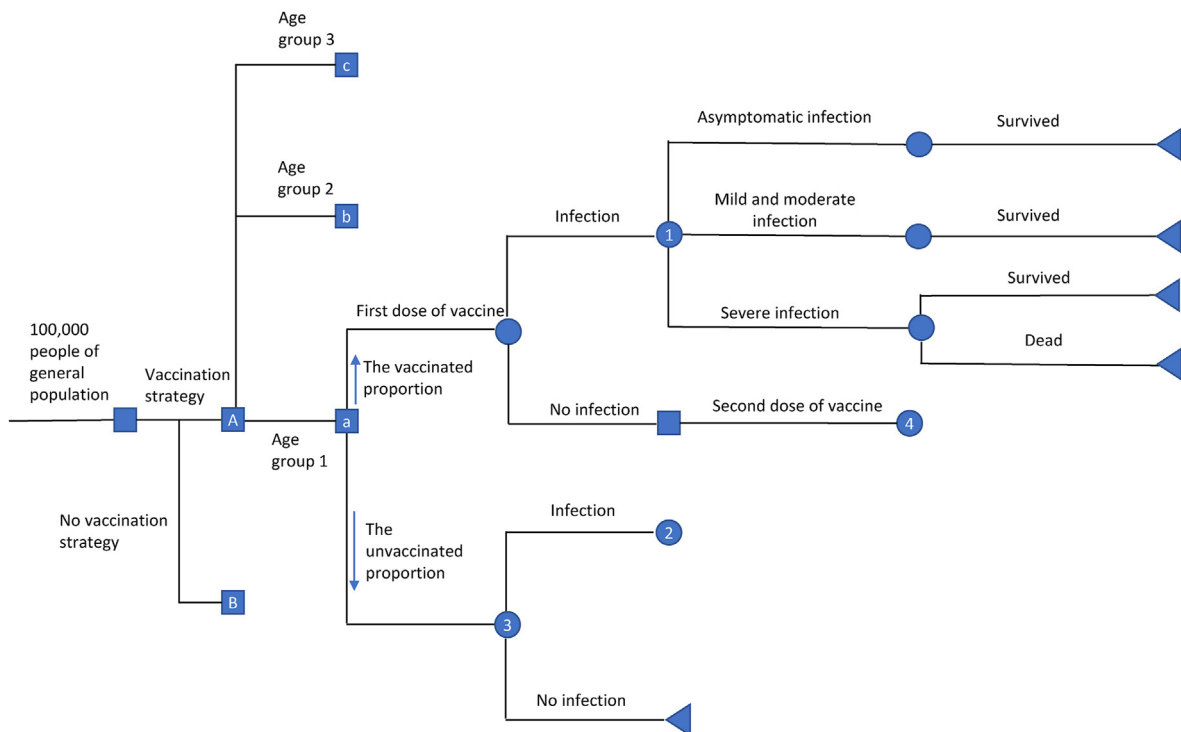


Fig. 1. The structure of the decision tree model. The sub-branch of each strategy was populated with 100,000 susceptible individuals at the beginning. Nodes A and B share the same structure. Nodes b and c follow the pattern of node a but had different values for some parameters. Chance node 2 replicates the pattern of chance node 1, whereas chance node 4 replicates chance node 3.

In the vaccination strategy, 50% of individuals received the first shot on day 1, which was followed by a 28-day interval. During this interval, individuals might become infected or remain uninfected. The infected people were further classified as asymptomatic cases, mild and moderate cases, or severe and critical cases. We used the proportions from the placebo arm of the NCT04510207 clinical trial as the corresponding inputs in the model (Table 1). It was further specified in the model that asymptomatic cases incurred neither clinical consequences nor medical costs whereas the mild and moderate cases had to endure an average symptomatic duration that, depending on the region, varied from 11 to 21 days before recovery (Table 1) (Pongpirul et al., 2020; Lam et al., 2020; Lim et al., 2020; Qi, 2020). Data on the durations from mainland China were taken as inputs for countries and regions where such evidence was missing. By contrast, severe and critical cases could either recover or die. Accordingly, the duration of staying in severe and critical conditions and the probability of dying afterwards also varied across regions (Table 1) (Chew et al., 2020; Lam et al., 2020; Lim et al., 2020; Pongpirul et al., 2020; Qi, 2020; The Novel Coronavirus Pnc, 2020). For individuals remaining uninfected 28 days after the first shot, the second dose was administered. These individuals could either remain healthy throughout the rest of the year or become infected and go through the above-mentioned disease course.

In the no vaccination strategy, individuals were confronted with the background attack rate of the pandemic without any artificial immunization, but otherwise followed the same set of clinical courses once infected.

To account for heterogeneity in health utility, potential QALY loss related to mortality, and productivity loss across subpopulations, we stratified the model by three age groups including <20 years, 20–59 years, and ≥60 years, the distributions of which were obtained from the population projection of the United Nations (United Nations and D.o.E.a.S, 2019). The weighted average of the outcomes across groups was taken using the age distributions of the population.

2.4. Attack rate

It is challenging to define the true attack rate of COVID-19 since all observed rates were subject to public health interventions to some extent. As such, we deferred to the pivotal clinical trial of HB02 in the base case. Specifically, the 1-year probability of infection was transformed from the per person-year incidence rate in the NCT04510207 clinical trial using the declining exponential approximation of life expectancy (DEALE) method (Al Kaabi et al., 2021; Beck et al., 1982). The method calculates the 1-year probability of infection as

$$p = 1 - \exp(-r),$$

In which p was the one-year attack rate and r was the incidence rate in person-year. For the 4-week between-dose break and the rest of the year after the second dose, the corresponding attack rates among the vaccinated individuals were transformed from the one-year probability, which were calculated as:

$$\begin{aligned} 28\text{-day probability}_{\text{unvaccinated}} &= 1 - \exp(-(-28/365) \times \ln(1-p)), \\ 28\text{-day probability}_{\text{vaccinated}} &= (1 - VE_{1st\ dose}) \times 28\text{-day probability}_{\text{unvaccinated}}, \\ 337\text{-day probability}_{\text{unvaccinated}} &= 1 - \exp(-(-337/365) \times \ln(1-p)), \\ 337\text{-day probability}_{\text{vaccinated}} &= (1 - VE_{2nd\ dose}) \times 337\text{-day probability}_{\text{unvaccinated}}, \end{aligned}$$

where $VE_{1st\ dose}$ was the VE after the first dose, $VE_{2nd\ dose}$ was the VE after the second dose, and \ln represented the natural logarithmic function.

2.5. Costs

Both direct costs and indirect costs were taken into account in the present study. Direct costs included vaccination program costs and medical costs, of which the former encapsulated the acquisition, cold chain freight, refrigerator storage, and administration of vaccines whereas the latter referred to medical treatment costs. Productivity loss due to days spent in sickness and premature death before retirement were quantified as indirect costs.

The price of each dose of HB02 was based on the price quote by its manufacturer for the Nepal government, in which each dose had a price tag of US\$16.23 or roughly CN¥105 (1 USD = 6.5 RMB) (Shrestha and Giri, 2021). To be consistent with the literature, the freight costs were assumed to be 6% of vaccine acquisition costs (Chen et al., 2019). Also, the costs of refrigerating were calculated per the WHO recommendations whereas the administration costs were taken from previous studies in different countries (World Health Organization, 2002). Using the WHO recommended approach, a wastage rate of 5% and a buffer stock of 25% of the total amount were assumed (World Health Organization, 2002), following which the quantities in the following equations were calculated sequentially to estimate the cold storage costs per dose:

$$\begin{aligned} \text{Cohort demand of doses} &= \text{population of cohort} \times \text{vaccination rate} \times (1 / (1 - \text{wastage rate})) \times (1 + \text{buffer stock proportion}) \\ \text{Storage volume} &= \text{Cohort demand of doses} \times \text{volume per dose} \times \text{space factor} \end{aligned}$$

Table 1
Base case parameters used in the model.

Parameter	Hong Kong, China	Indonesia	mainland China	Philippines	Singapore	Thailand	Distribution	Source
Proportion of <20 years	0.16	0.34	0.23	0.40	0.17	0.23	Not in PSA-	Department of Economic an (2019)
Proportion of 20–59 years	0.58	0.55	0.59	0.52	0.62	0.58	Not in PSA	Department of Economic an (2019)
Proportion of ≥60 years	0.26	0.10	0.17	0.09	0.21	0.19	Not in PSA	Department of Economic an (2019)
Overall vaccine efficacy (second vaccination)	68.7%	68.7%	68.7%	68.7%	68.7%	68.7%	Beta	(Al Kaabi et al., 2021; Palacios et al., 2021; World Health Organization, 2021b)
Vaccine efficacy after the 1st dose	Half of full efficacy	Half of full efficacy	Half of full efficacy	Half of full efficacy	Half of full efficacy	Half of full efficacy	Not in PSA	Assumption
Vaccine efficacy against mild cases	69.9%	69.9%	69.9%	69.9%	69.9%	69.9%	Beta	(Al Kaabi et al., 2021; Palacios et al., 2021; World Health Organization, 2021b)
Vaccine efficacy against severe cases	100%	100%	100%	100%	100%	100%	Not in PSA	(Al Kaabi et al., 2021; Palacios et al., 2021; World Health Organization, 2021b)
Vaccination rate	50%	50%	50%	50%	50%	50%	Beta	Assumption
Freight rate	6%	6%	6%	6%	6%	6%	Gamma	Chen et al. (2019)
Wastage rate	5%	5%	5%	5%	5%	5%	Gamma	World Health Organization (2002)
Buffer stock	25%	25%	25%	25%	25%	25%	Gamma	World Health Organization (2002)
Volume per dose (cm ³)	89.78	89.78	89.78	89.78	89.78	89.78	Gamma	Imputed
Space factor	4.5	4.5	4.5	4.5	4.5	4.5	Gamma	Tao et al. (2009)
Storage volume of vaccine (cm ³ per refrigerator)	898560	898560	898560	898560	898560	898560	Gamma	World Health Organization (2021c)
Costs of refrigerator (per refrigerator, US\$)	403.39	403.39	403.39	403.39	403.39	403.39	Gamma	Jiang et al. (2011)
Vaccination campaign duration	183	183	183	183	183	183	Gamma	Assumption
Vaccine acquisition costs/dose (US\$)	16.34	16.34	16.34	16.34	16.34	16.34	Gamma	Shrestha and Giri (2021)
Administration costs per dose (US\$)	1.68	0.60	4.06	0.95	2.03	0.60	Gamma	(Chotivitayatarakorn et al., 2010; The Reuters Institute Dig, 2021b; Thompson and DuintjerTebbens, 2014; Wilopo et al., 2009; Wu et al., 2016)
Direct medical costs of mild and moderate cases (US\$)	19146	3553	4552	1881	8630	4320	Gamma	(Coins.ph. Cost ofD-1, 2021; Indonesia. Biaya Per, 2021; Thai Public Broadcasting., 2021; Patria Jati et al., 2020; Li et al., 2020; Hospital Authority. Fees, 2021; Planning and Development and, 2019)
Direct medical costs of severe and critical infection (US\$)	63764	9246	15160	11247	12658	14386	Gamma	(Coins.ph. Cost ofD-1, 2021; Indonesia. Biaya Per, 2021; Thai Public Broadcasting., 2021; Patria Jati et al., 2020; Li et al., 2020; Hospital Authority. Fees, 2021; Planning and Development and, 2019)
Labor force participation rate	59.50%	68.19%	68.19%	59.44%	77.86%	66.96%	Not in PSA	(The World Bank. Labor for, 2021; Census and Statistics Dep, 2021; Statista. Demographics: L, 2020)
Annual salary (US\$)	48713	4136	10504	3486	65233	7807	Not in PSA	The World Bank.P per c (2021b)
Proportion of asymptomatic infection	0.16	0.16	0.16	0.16	0.16	0.16	Beta	Al Kaabi et al. (2021)
Proportion of mild and moderate cases	0.82	0.82	0.82	0.82	0.82	0.82	Beta	Al Kaabi et al. (2021)
Proportion of severe and critical infection	0.02	0.02	0.02	0.02	0.02	0.02	Beta	Al Kaabi et al. (2021)
Probability of recovery of severe and critical patients	0.88	0.88	0.88	0.88	0.89	0.88	Beta	(Chew et al., 2020; Epidemiology Working Grou, 2020; Pongpirul et al., 2020; Surendra et al., 2021)
Utility of Iranian population	0.790	0.790	0.790	0.790	0.790	0.790	Beta	Emrani et al. (2020)
Utility of population <20 years	0.980	0.971	0.974	1.000	0.997	0.983	Beta	(Abdin et al., 2015; Castillo-Carandang et al., 2018; Purba et al., 2018; Sun et al., 2011; Szende et al., 2014; Wong et al., 2018)
Utility of population 20–59 years	0.801	0.791	0.828	0.889	0.955	0.801	Beta	(Abdin et al., 2015; Castillo-Carandang et al., 2018; Purba et al., 2018; Sun et al., 2011; Szende et al., 2014; Wong et al., 2018)

(continued on next page)

Table 1 (continued)

Parameter	Hong Kong, China	Indonesia	mainland China	Philippines	Singapore	Thailand	Distribution	Source
Utility of population ≥ 20 years	0.763	0.769	0.688	0.860	0.899	0.747	Beta	(Abdin et al., 2015; Castillo-Carandang et al., 2018; Purba et al., 2018; Sun et al., 2011; Szende et al., 2014; Wong et al., 2018)
Utility of severe COVID-19 cases in Iran	0.607	0.607	0.607	0.607	0.607	0.607	Beta	Arab-Zozani et al. (2020)
Utility decrement of mild COVID-19 cases	0.051	0.051	0.051	0.051	0.051	0.051	Beta	GBD 2017 Disease and Injury incidence and prevalence collaborators (2018)
Utility decrement of severe COVID-19 cases	0.183	0.183	0.183	0.183	0.183	0.183	Beta	Imputed
Disease duration of mild and moderate cases (days)	14	14	14	14	21	11	Gamma	(Lam et al., 2020; Lim et al., 2020; Pongpirul et al., 2020; Qi (2020))
Disease duration of severe and critical cases before recovery (days)	21.6	20	20	20	28	19	Gamma	(Lam et al., 2020; Lim et al., 2020; Pongpirul et al., 2020; Qi (2020))
Disease duration of severe and critical cases until death (days)	11	6	11	11	11	11	Gamma	(Surendra et al., 2021; Wang et al., 2020b)
Injection interval (days)	28	28	28	28	28	28	Gamma	The Reuters Institute Dig (2021b)
Vaccination rate	0.50	0.50	0.50	0.50	0.50	0.50	Beta	Assumption
Incidence of COVID-19 (person-year)	0.0547	0.0547	0.0547	0.0547	0.0547	0.0547	Beta	Al Kaabi et al. (2021)
Annual probability of COVID-19 infection	0.0532	0.0532	0.0532	0.0532	0.0532	0.0532	Beta	calculated
Discount rate	3%	3%	3%	3%	3%	3%	-	-

Abbreviation: PSA, probabilistic sensitivity analyses.

Demand of refrigerator = Storage volume / Storage volume per refrigerator

Cost of refrigerator per dose = Demand of refrigerator \times price of a refrigerator/ demand of vaccine/number of batches delivered

where *space factor* represented the ratio of refrigerator volume to the volume of vaccines the refrigerator hosted. In the present analysis, a package volume per dose of 89.78 cm³ was used based on authors' measurement of the box of a HB02 vial. Using data from a cold chain capacity estimation study, the space factor was set at 4.5 (Tao et al., 2009). In addition, the storage volume per refrigerator was benchmarked at 8.99 m³ while its price was extracted from an economic evaluation of pneumococcal vaccination in China and inflated to 2020 (Jiang et al., 2011; World Health Organization, 2021c). Since the refrigerators could be considered as reusable devices, the corresponding costs were further divided by 183 with the assumption that the vaccination campaign of two doses per recipient was completed in half a year and the refrigerator capacity would just meet the daily distribution need. Due to an absence of relevant estimates and reliable data to generate such estimates, an assumption was inevitable and was subject to sensitivity analysis.

Medical treatment costs depended on the severity of patients and were, therefore, classified as costs of mild and moderate cases and costs of severe and critical cases, the input data of which were extracted from the literature and the websites of relevant government bodies or health insurance agencies (Lim et al., 2020; Li et al., 2020a, 2020b; Hong Kong Hospital Author, 2017; Coins.ph. Cost of d-1, 2021; Indonesia. Biaya Per, 2021; Thai Public Broadcasting., 2021; Patria Jati et al., 2020). However, the COVID-19 treatment costs information was not available for Hong Kong SAR. Also, the by-severity information on COVID-19 treatment costs was not available for Thailand. For Hong Kong, the costs of severe and critical cases were estimated using the average costs of all-cause hospitalizations in Hong Kong and the ratio of the costs of severe and critical COVID-19 cases to the average costs of all-cause hospitalizations in mainland China (Hong Kong Hospital Author, 2017). On top of that, the costs of mild and moderate cases were further estimated using the ratio of the costs of mild and moderate cases to that of severe and critical cases in mainland China (Li et al., 2020a, 2020b). Specifically, the following formula was used:

Costs of severe and critical cases in Hong Kong SAR = Costs of severe and critical cases in mainland China / Average daily inpatient costs in mainland China \times Average daily inpatient costs in Hong Kong SAR

Costs of mild and moderate cases in Hong Kong SAR = Estimated costs of severe and critical cases in Hong Kong SAR \times Costs of mild and moderate cases in mainland China / Costs of severe and critical cases in mainland China

For Thailand, the by-severity cost estimation followed the same approach as that for Hong Kong except that the overall average costs of COVID-19 cases were directly taken from the literature (Indonesia. *Biaya Per*, 2021; Thai Public Broadcasting., 2021). Even more, the costs of mild and moderate patients in Indonesia were estimated using the mid-point of the costs of “low level severity” Covid-19 patients and those of the “moderate level severity” patients (Patria Jati et al., 2020).

The accrual of productivity loss was based on the human capital costs approach, in which daily labor compensation rate was first multiplied by the labor participation rate of each age group and then scaled by sickness time and mortality, if any (Pongpirul et al., 2020; Lam et al., 2020; Lim et al., 2020; Qi, 2020; The World Bank. *Labor for*, 2021; Census and Statistics Dep, 2021; Statista. *Demographics: L*, 2020). For countries and regions of which the compensation information was absent, GDP per capita was used in lieu of the former (National Bureau of Statis, 2021; The World Bank. *P per c*, 2021a). Of note, the productivity loss of the age group of ≥ 60 years and older was not considered, whereas the age group of < 20 years only accrued productivity loss over the period beyond 16 years old.

All input values related to costs are listed in Table 1 and all costs were represented in 2021 US\$.

2.6. Health outcomes and benefits

As of the submission of this study, health state utility values (HSUV) associated with COVID-19 have only been estimated for severe and critical cases, which was conducted in the setting of Iran (Arab-Zozani et al., 2020). To estimate the disutility of severe and critical COVID-19 cases for each country and region, the weighted average of the HSUVs of severe and critical cases evaluated in Iran was calculated and subtracted from the utility values of the Iranian general population (Arab-Zozani et al., 2020; Emrani et al., 2020). For mild and moderate cases, the disutility value of acute mild episodes of respiratory infections from the 2017 WHO Global Burden of Diseases study was used (GBD 2017 Disease and Injury incidence and prevalence, 2018). The QALY loss associated with each terminal node were then accrued over the corresponding duration (Abdin et al., 2015; Castillo-Carandang et al., 2018; Purba et al., 2018; Sun et al., 2011; Szende et al., 2014; Wong et al., 2018). Of note, simply accruing outcomes over the 1-year time horizon would severely underestimate the benefit of vaccination since a substantial proportion of health benefit was avoided QALY loss due to reduced mortality. To comprehensively capture the health benefit, the QALY loss associated with each COVID-19 death was attached to deceased individuals in the model. The single-index QALY loss reflected discounted future QALYs an individual would have endured had the individual not died of the disease. To maintain consistency across countries and regions, the relatively commonly used annual discount rate of 3% was used (Haacker et al., 2020).

When there were no dominant strategies, incremental cost-effectiveness ratios (ICERs) were calculated by dividing the incremental costs by incremental QALYs. Cost-effective thresholds (CETs) of once the gross domestic product (GDP) per capita were used (Robinson et al., 2016). When there were dominant strategies, net monetary benefit (NMB) was evaluated instead. The CETs were used to monetize the incremental QALYs in these situations.

2.7. Scenario and sensitivity analyses

Given the uncertainty over the progress of the pandemic and a lack of information on a range of factors related to both the disease and the vaccines, it was critical to account for alternative scenarios and inaccuracy of parameters in our analyses. Therefore, several scenario analyses and deterministic sensitivity analyses were conducted. In the first scenario analysis, the efficacy profile of HB02 was used in lieu of the meta-analyzed estimates (Al Kaabi et al., 2021). Similarly, the efficacy profile of CoronaVac was used in a second scenario analysis (Al Kaabi et al., 2021; Palacios et al., 2021; World Health Organization, 2021b). At least three clinical trials investigated the efficacy of CoronaVac, which were conducted in Brazil, Indonesia, and Turkey, respectively (World Health Organization, 2021b). Data from the three trials were pooled to estimate the VE of CoronaVac against symptomatic cases using a second meta-analysis in the current study. The pooled estimate of VE against symptomatic cases was 67.9% (Fig. S2). Also, CoronaVac was 83.70% efficacious against moderate infections and 100% efficacious against severe infections (Costa, 2021). Similar to the base case, these efficacy numbers were taken into the decision tree model simultaneously by applying the numbers to the corresponding chance nodes. More, the price of CoronaVac was set at US\$13.57 per dose, which was based on the agreement between its manufacturer and the Indonesian government (The Reuters Institute Dig, 2021a). Whereas the rates of adverse events associated with the inactivated vaccines were not necessarily higher than the placebo, the third scenario analysis accounted for the disutility of injection-related mild and moderate adverse events such as injection site pain and headache (Al Kaabi et al., 2021). Although the incidence of injection-related side effects was relatively common (about 45%) (Al Kaabi et al., 2021), the impacts of such events were considered transient. In the fourth scenario analysis, a series of mutually exclusive vaccinating strategies were compared. Namely, the strategies were no vaccination, vaccinating > 60 years old people only, vaccinating every 20 years old and above, and vaccinating everyone. This set of analysis allowed the identification of an optimal strategy among the alternatives.

In a set of exploratory analyses, the incidence rate and the vaccination rate were each toggled over a continuum. The output of the analyses were contour graphs showing the frontier of incidence-vaccination combinations over which the vaccination strategies were cost-effective at the once the GDP per capita threshold.

To examine the impacts of parameter uncertainty, the inputs were varied upward and downward in one-way sensitivity analyses (OWSAs). Among these, most parameters were changed by 20% whereas vaccination rate, disease incidence,

and VE were subject to greater variations to reflect greater uncertainty. In addition, utility scores changed by 0.1 and the discount rate spanned from 0% to 5%. The OWSAs were also conducted in the scenario analyses featuring the profiles of HB02 and CoronaVac. More, probabilistic sensitivity analyses were conducted by resampling the parameters from their respective distributions (Briggs et al., 2012). Costs and healthcare utilization parameters were assumed to follow gamma distributions whereas proportions, probabilities, and ratios were assumed to follow beta distributions (Campbell et al., 2015). Empirical estimates of standard errors were used if available. When such estimates were absent, the standard errors were assumed to be 10% of the point estimates. The distributions of the parameters that were subject to PSA are shown in Table 1.

2.8. Model validation

The internal validity of the decision tree model was examined by setting the VE inputs to zero and examining whether the incremental costs and QALYs were zero. Since the vaccination and no vaccination routes were programmed separately, results otherwise would suggest programming errors in the model.

2.9. Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research. The study was reported per the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement (Husereau et al., 2013).

3. Results

For the cohort of 100,000 individuals, the strategy of vaccinating 50% of the population saved 105.18, 98.15, 99.70, 60.48, 112.00, and 103.47 QALYs compared with no vaccination in Hong Kong SAR, Indonesia, mainland China, Philippines, Singapore, and Thailand, respectively. Also, the vaccination strategy saved US\$40.26 million, US\$5.26 million, US\$7.60 million, US\$5.91 million, US\$21.33 million, and US\$7.18 million correspondingly. Accordingly, the vaccination strategy was consistently dominant with the incremental QALYs and cost savings amounted to NMBs of US\$45.38 million, US\$5.66 million, US\$8.65 million, US\$10.20 million, US\$28.63 million, and US\$7.98 million in the abovementioned countries and regions, respectively. The base-case results are presented in Table 2.

The base-case and OWSA results of the scenario analyses using HB02 and CoronaVac profiles separately are illustrated in supplementary materials Fig. S3 and Fig. S4. When the efficacy profiles of HB02 and CoronaVac were used, the NMB estimates and the patterns of change following parameter variations resembled those of the base case. The results of the scenario analyses of vaccination strategies by age group are summarized in supplementary materials Table S2. For all countries and regions, the strategy of vaccinating everyone was the optimal strategy whereas other strategies were dominated.

When the incidence and vaccination rates were varied semi-continuously, vaccinating the population generated NMB when the incidence rate was above 0.02/person-year in all jurisdiction regardless of the vaccination rates. In Hong Kong SAR and Indonesia, the full-population vaccination strategy generated net benefit even when the incidence rate was as low as 0.005/person-year. More importantly, the amount of NMB was increasing in both incidence rate and vaccination rate. For example, the NMBs under combinations of relatively high incidence and vaccination rates was generally magnitudes higher than the counterparts under combinations of low levels of incidence and vaccination rates. The contour lines demonstrating the impact of the covariation of incidence and vaccination rates on NMB are illustrated in Fig. 2.

The OWSA results of the main analysis are depicted in Fig. 3. Across all countries and regions, incidence and vaccination rates had relatively substantial impacts on the results. However, the vaccination strategy carried nontrivial net benefit in all variations. The PSA results are wrapped up as cost-effectiveness acceptability curves (CEACs) in supplementary materials Fig. S6. Since the vaccination strategy was dominant in all repetitions of all jurisdictions, the probability of vaccination being cost-effective was 100% for any non-zero cost-effective thresholds.

Table 2

Base-case results.

	Hong Kong SAR, China	Indonesia	mainland China	Philippines	Singapore	Thailand
Costs without vaccination (2021 US\$)	96,007,188	17,085,078	23,069,424	15,469,980	53,274,439	21,366,927
Costs with 50% of the population vaccinated (2021 US\$)	55,751,750	11,828,787	15,470,837	9,560,668	31,947,401	14,189,918
QALY loss without vaccination	-216.71	-202.29	-205.47	-124.47	-231.12	-213.03
QALY loss with 50% of the population vaccinated	-111.53	-104.14	-105.77	-63.99	-119.12	-109.56
Incremental costs (2021 US\$)	-40,255,438	-5,256,290	-7,598,587	-5,909,312	-21,327,039	-7,177,008
Incremental QALYs	105.18	98.15	99.70	60.48	112.00	103.47
ICER	dominant	dominant	dominant	dominant	dominant	dominant
NMB (2021 US\$)	45,379,143	5,662,212	8,645,824	10,196,996	28,632,981	7,984,741

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit.

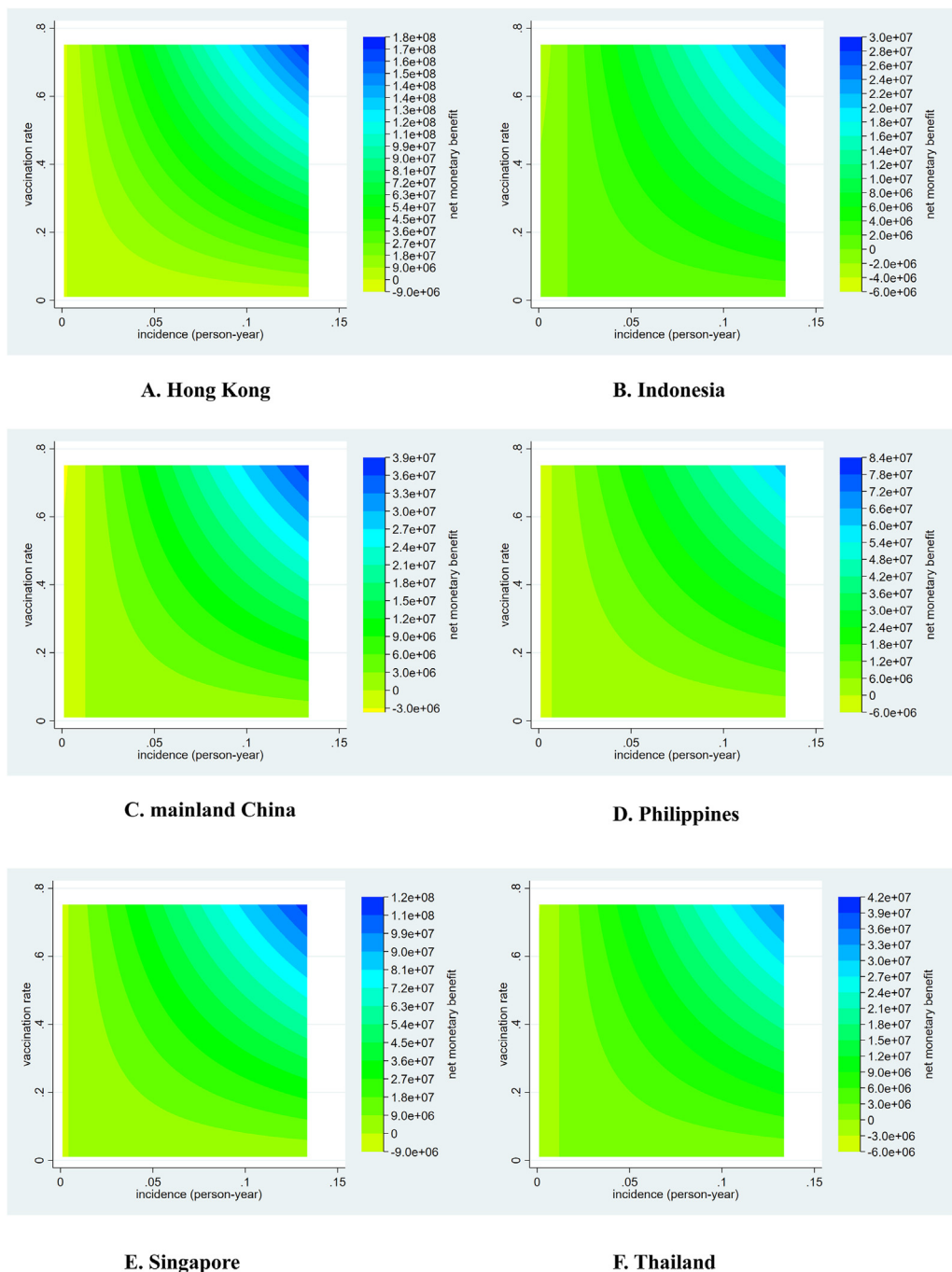


Fig. 2. The net monetary benefit of vaccination using different incidence and vaccination rate combinations in each country and region. For each jurisdiction, one of the curves (denoted as 0) represented the frontier that distinguishes the cost-effective versus the cost-ineffective incidence-vaccination combinations.

4. Discussion

In the present study, decision-tree models were used to analyze the cost-effectiveness of vaccinating 50% of the population using inactivated COVID-19 vaccines in Hong Kong SAR, Indonesia, mainland China, Philippines, Singapore, and Thailand. The results suggested that the vaccination strategy was not only cost-effective but also created sizeable NMB. Also, whereas the deterministic results were robust to parameter variations, the magnitude of NMB increased with the incidence of COVID-19 and the population coverage of vaccines. To our knowledge, the present study represented one of the first efforts to analyze the cost-effectiveness of inactivated COVID-19 vaccines in Western Pacific and South East Asian regions.

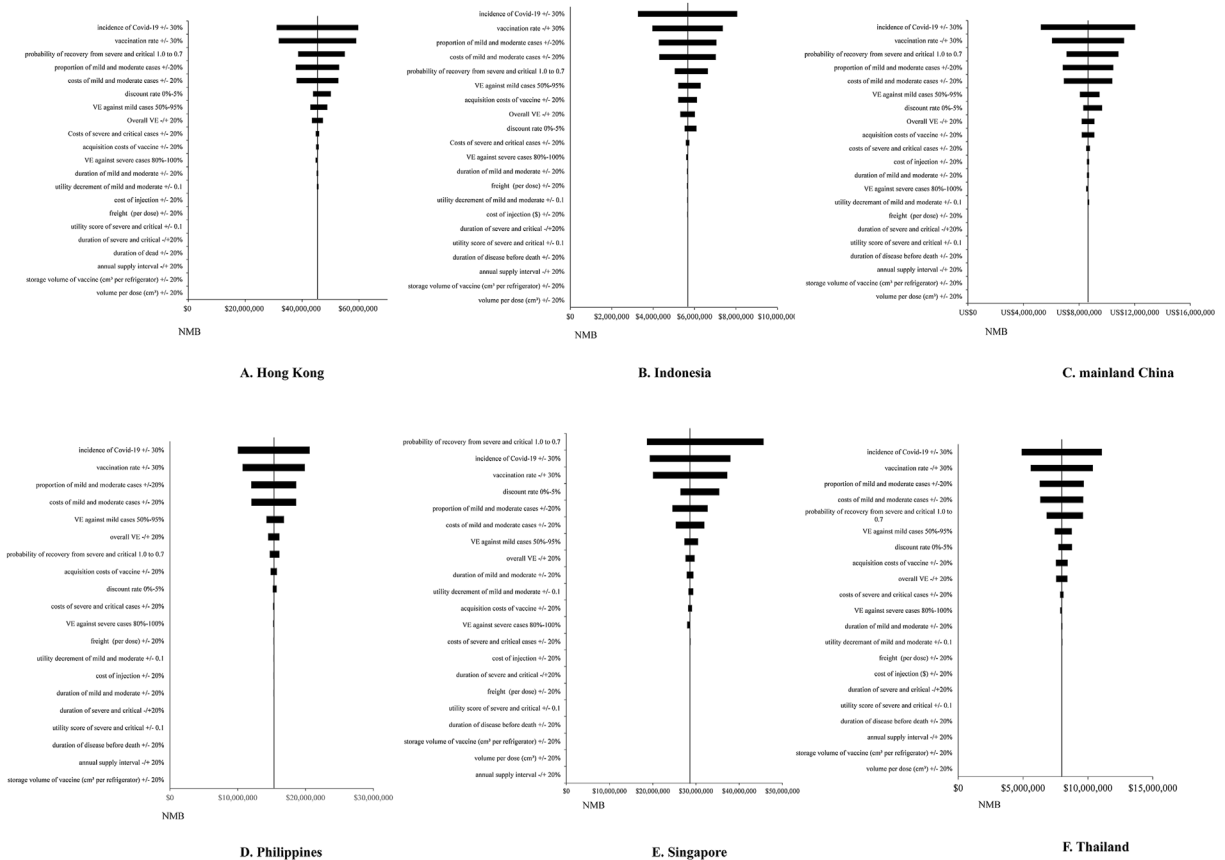


Fig. 3. Tornado graphs of one-way sensitivity-analyses. Results were robust to parameter variations.

The results entailed important policy implications for the protection of the population against COVID-19 in the low-, middle-, and high-income countries in Western Pacific and South East Asian regions. Inactivated COVID-19 vaccines are relatively easy to reserve and deliver due to relatively manageable distribution conditions (Baraniuk, 2021; Rostad and Anderson, 2021), thereby posing themselves as near-ideal candidates for mass vaccination campaigns in limited resource settings. However, the total resource consumption still needs to be evaluated in relation to the outputs of the investment. The present findings indicate that vaccinating half of the population is cost-effective in the target countries and regions, and the benefit of vaccination increases with both the incidence rate and the vaccination rate. Therefore, engaging inactivated vaccines for COVID-19 immunization programs may be a viable approach to neutralize the pandemic in the target countries and regions.

When evaluating the cost-effectiveness of COVID-19 vaccines, a parameter of pivotal importance is the intensity of viral circulation. In some parts of the Western Pacific and South East Asian regions, the pandemic has been controlled to a minimum with enduring and heavy non-pharmaceutical interventions (NPIs). In such settings, vaccination would not be impactful if the behavior-regulating NPIs are not to be lifted. However, the present analysis aimed to shed light on the economic profiles of inactivated vaccines to the extent that vaccination was part of pandemic-exiting strategies to restore normal activities such that a disease attack rate representing the natural state without NPIs and vaccination should be taken as the context. The true rate could not be estimated since most affected countries locked down and implemented mask-wearing policies to different degrees. As such, we relied on the attack rate in one of the clinical trials of inactivated vaccines in the based case and explored a wide range of additional scenarios, in which the value of inactivated vaccines was confirmed. An additional implication of the uncertainty of epidemic intensity relates to the choice of modeling method. If the true natural epidemic history was known, a dynamic transmission model could be used to reproduce the epidemic curve, following which the health and economic impacts of vaccination could be assessed. Since the true epidemic intensity and the corresponding model parameters are unknown, there is no guarantee that a dynamic transmission model provides more reliable information than static models when evaluating vaccination. Although it is tempting to reason that the epidemic situation during the first very few days after the initial outbreak could be used to inform the epidemic parameters, such an approximation would unlikely reflect the post-pandemic situation due to institutional changes in human knowledge and the variation of the virus itself.

The results of the present study should be interpreted with several caveats. First, the present study relied on several assumptions for input data as with most modeling exercises. This is especially inevitable for a relatively new disease such as COVID-19. For example, the HSUVs of various COVID-19 disease states are severely under-investigated. Second, the VE of the vaccines was tested against currently circulating strains of the virus, yet the virus is ever-mutating, creating uncertainty in the effectiveness of the vaccines in future. Therefore, to what extent the results can be extrapolated is unknown. Third, the analysis did not evaluate the vaccines in terms of both the long-term evolution of the pandemic and possible lasting immunity. There is a dearth of evidence on both by far. Despite these limitations, the deterministic implications of the analysis with regard to the benefits of vaccination provided important insights on the value of population immunization using inactivated vaccines in the target countries and regions.

5. Conclusions

Population immunization programs using inactivated COVID-19 vaccines may be not only cost-effective but also cost-saving in Hong Kong SAR, Indonesia, mainland China, Philippines, Singapore, and Thailand. As such, inactivated vaccines should be considered for mass vaccination programs in these jurisdictions.

Declarations

Institutional Review Board Statement.

Not applicable. The submitted work is a modeling study that used existing publicly available data.

Data availability

The data analyzed during the study are presented in the article and its supplementary materials. The program and code that were used in the present study have been provided for editorial and peer review and are available from the corresponding author upon reasonable requests.

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Author contributions

Conceptualization, design, data collection, analysis, programming, and writing: Y.J.; data collection, analysis and manuscript revision: D.C.; manuscript revision: S.S.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.idm.2021.12.002>.

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