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Research article

Prioritizing COVID-19 vaccination. Part 2: Real-time comparison between single-dose and double-dose in Japan

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Abstract: Japan successfully implemented a mass vaccination program for coronavirus disease 2019 (COVID-19), immunizing more than 1 million persons a day by July 2021. Given the COVID-19 vaccination capacity limitations, an urgent question was raised regarding whether it would be better to (i) complete double-dose COVID-19 vaccination among healthcare personnel and older adults before beginning double-dose vaccination of younger adults (double-dose strategy) or (ii) allocate a single dose of COVID-19 vaccine to all adults regardless of age before administering the second dose (single-dose-first strategy). We used an age-structured susceptible-infectious-recovered (SIR) compartment model to compare the effectiveness of possible COVID-19 vaccination strategies and the length of public health and social measures (PHSM) to minimize the cumulative COVID-19 disease risk and death toll. Our results indicate that if the single-dose-first strategy was taken, an estimated total of 1,387,078 persons, i.e., 263,315 children, 928,518 young adults, and 195,245 older adults, would develop COVID-19, resulting in 15,442 deaths. In contrast, if the double-dose strategy was taken instead, an estimated total of 1,900,172 persons, i.e., 377,107 children, 1,315,927 young adults, and 207,138 older adults, would develop COVID-19, yielding 17,423 deaths. Real-time investigation favored the disease transmission blocking option, i.e., single-dose vaccination strategy. Applying the single-dose-first strategy should yield a smaller epidemic size than applying the double-dose strategy; however, for both strategies, PHSM will be essential by the time second-dose COVID-19 vaccination is complete among all adults.

Keywords: immunization; mathematical model; basic reproduction number; pandemic; herd immunity; allocation strategy

1. Introduction

Japan started its vaccination program for coronavirus disease 2019 (COVID-19) in February 2021, using messenger RNA (mRNA) COVID-19 vaccines and first prioritizing healthcare personnel. The country had a plan to host the Tokyo Olympic Games, which had been postponed for 1 year from 2020 owing to the COVID-19 pandemic, beginning in late July 2021. Fueled by the need to protect at least the higher risk population of adults aged 65 years or older by that time, Japan successfully vaccinated more than 1 million persons a day, a speed of immunization that was unprecedented in the history of Japan. Given the available COVID-19 vaccination capacity, a critical study question was whether to implement single-dose vaccination to as many people as possible or to adopt a double-dose vaccination strategy targeting high risk populations to firmly protect older adults and people with a comorbidity or at risk of severe complications from COVID-19, which we have discussed at length in Part 1 [1].

Owing to the high basic reproduction number, i.e., average number of secondary cases caused by a single primary case in a fully susceptible population, and the substantial infection fatality risk (IFR), i.e., the risk of death among all infected individuals, especially among older adults, of COVID-19, it would have been ideal to vaccinate the entire population in advance of the Olympic Games and achieve herd immunity; however, the COVID-19 vaccine stocks and the available time for vaccinating citizens were both limited. In the previous study of this study series, we explored the question of which COVID-19 strategy is better by using final size equation [1], similarly to earlier studies on pandemic influenza [2–4]. However, the vaccination in that type of approach was modeled in a static manner. When the fixed capacity of vaccination per unit time is known (as is the case in the present study), it would be valuable to explore the prioritization question (i.e., single dose vs double dose), employing a dynamic modeling approach.

An urgent question was raised regarding whether it would be better to (i) complete double-dose COVID-19 vaccination among healthcare personnel and older adults before beginning double-dose vaccination of younger adults (double-dose strategy) or (ii) allocate a single dose of COVID-19 vaccine to all adults regardless of age before administering the second dose (single-dose-first strategy). This question is raised, because vaccination has two different effects, i.e., (i) preventing disease and preventing death from disease, and (ii) preventing secondary transmission and offer indirect protection. Depending on which aspect to give a greater weight, theoretically optimal strategy can vary.

Several previous studies have shown that adults of older ages or with underlying comorbidities [5–7], or health-care personnel [8–10] should be prioritized for COVID-19 vaccination to efficiently lower the overall mortality and years of life lost from COVID-19. Other studies have shown that vaccination against COVID-19 of younger essential workers or the implementation of COVID-19 transmission-interrupting strategies would be superior to simply widening COVID-19 vaccination coverage among the older adult population [11,12]. One study demonstrates that vaccine-rollout speed is crucial for earlier suppression of the viral epidemic [13]. At the same time, the implementation of other public health measures, i.e., public health and social measures (PHSM), has been considered essential [14,15], especially when considering the emergence of more transmissible severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern [16–18]. For realistic argument of the COVID-19 vaccination strategy, it has been vital to account for PHSM to be implemented during the course of COVID-19 vaccination program [19,20]. Modeling approaches have differed vastly, and, at minimum, a comparison between final size modeling and dynamic approach should be made.

Whereas our Part 1 study assumed that the COVID-19 vaccination was complete in the beginning of an epidemic, and thus, the vaccination impact was dealt with as a problem of initial values and associated parameters, in fact, it is vital to account for the dynamic recruitment of susceptibles for vaccination. In this Part 2 study, we aimed to compare single-dose and double-dose COVID-19 vaccination strategies using a dynamic epidemic model, i.e., an age-structured susceptible-infectious-recovered (SIR) model. Accounting for the actual capacity of daily COVID-19 vaccination administration in Japan and varying the length of PHSM, we aimed to identify the COVID-19 control strategy that yields the minimum SARS-CoV-2 infection risk and associated death toll.

2. Materials and methods

2.1. Datasets underlying our model

The population of Japan was divided into 15 five-year age groups, with the oldest age group composed of those aged 70 years or older. We derived the population data from the Statistics Bureau of Japan records as of February 2021, as summarized in Supplementary Table 1.

We used the age-specific IFR for SARS-CoV-2 infection that was calculated in a study conducted by Levin et al. [5] that systematically analyzed published estimates during the early COVID-19 pandemic period. Moreover, we used the age-dependent contact matrix and derived age-dependent transmission model for COVID-19 as described elsewhere [21,22]. The contact matrix for COVID-19 during the spring period of the COVID-19 pandemic in 2020 before the implementation of PHSM [23], which is available in the Part 1 study [1], was also used in the present study.

2.2. Data analysis procedures: Vaccine rollout strategies

Given the fixed capacity for COVID-19 immunizations per day, we compared the cumulative risks of SARS-CoV-2 infection and associated deaths between single-dose and double-dose COVID-19 vaccination strategies. In the case where COVID-19 vaccination coverage is elevated as a function of time, it is evident that all subjects eventually receive two doses of COVID-19 vaccine. We specifically assessed the superiority of the following two COVID-19 vaccination strategies: (A) prioritizing single-dose COVID-19 vaccination coverage in the population or (B) ensuring sufficient coverage of double-dose COVID-19 vaccination among older adults. The estimated outcomes of these two COVID-19 vaccination plans were compared.

Strategy A, which aims to elevate single-dose COVID-19 vaccination coverage, follows four steps: (i) older adults (aged 65 years or older) receive their first dose of COVID-19 vaccine, (ii) younger adults aged 20–64 years of age receive their first dose of COVID-19 vaccine, (iii) older adults receive their second dose of COVID-19 vaccine, and (iv) younger adults receive their second dose of COVID-19 vaccine (Figure 1A). In strategy B, which prioritizes achieving double-dose COVID-19 vaccination coverage among older adults, two crucial steps are taken: (i) first, older adults receive both their first and second doses of COVID-19 vaccine, 4 weeks apart, and (ii) subsequently, younger adults receive their first and second doses of COVID-19 vaccine at the same dose interval (Figure 1B). In both strategies, we assume that COVID-19 vaccination takes place at the rollout rate of a million doses per day. The abovementioned steps are considered as completed when the within group vaccination coverage reaches 100%.

While conducting COVID-19 vaccination, we also considered the contribution of PHSM, such as the declaration of a state of emergency, to temporarily reducing the reproduction number. For simplicity, we assumed that radical PHSM would be discontinued before the COVID-19 vaccination coverage reaches 100% of the population. In the absence of COVID-19 vaccination, we assumed that the effective reproduction number, *R*t, under PHSM was 1.1, whereas the *R*t after PHSM was assumed to be 2.5 [24,25]. Not necessarily continuing PHSM during COVID-19 vaccination, we also assumed that the intervention was lifted at the end of step (ii) in strategy A and step (i) in strategy B.

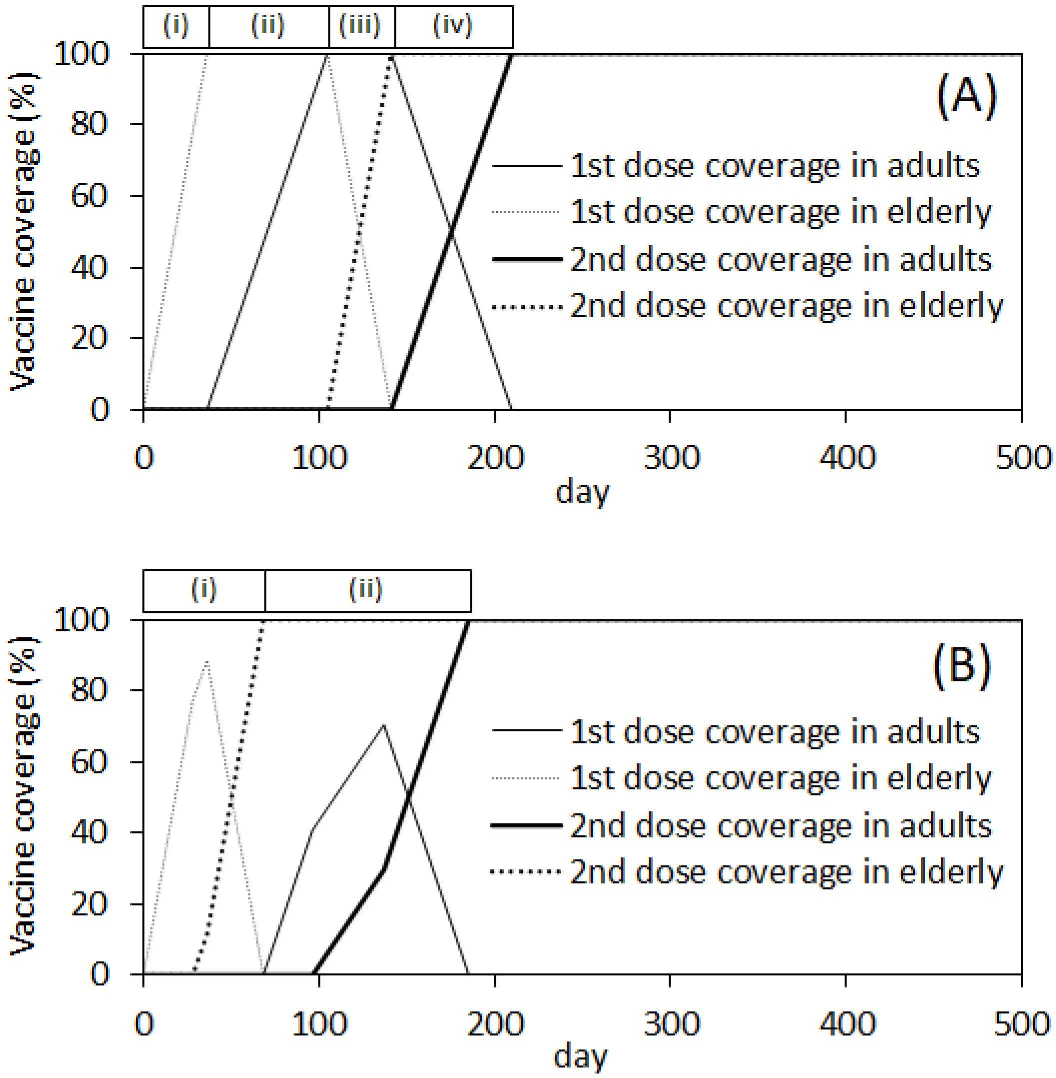

Figure 1. Two different vaccine rollout schedules at the rate of a million doses per day (A) Strategy A prioritizes an elevation of first-dose COVID-19 vaccination coverage by following these four steps: (i) older adults aged 65 years or older receive their first dose of COVID-19 vaccine, (ii) younger adults aged 20–64 years old receive their first dose of COVID-19 vaccine; (iii) older adults receive their second dose of COVID-19 vaccine, and (iv) younger adults receive their second dose of COVID-19 vaccine. (B) Strategy B prioritizes double-dose COVID-19 vaccination among older adults, proceeding with these two steps: (i) older adults receive their first and second doses of COVID-19 vaccine, 4 weeks apart, and (ii) younger adults receive their two doses of COVID-19 vaccine at the same dosage interval.

2.3. Epidemiological model and parameters

We use an SIR model to describe the epidemic dynamics of age-dependent COVID-19 transmission, dividing the population into 15 subgroups. Contact matrix **C** is a 15×15 matrix with its component C_{ij} denoting the relative frequency of a person in the age group j contacting a person in the age group i per unit of time (i and $j \in [1, 15]$). The contact was defined as the exchange of three Japanese sentences or a physical touch on the skin. The contact matrix during the spring period of the COVID-19 pandemic in 2020 was derived in the Part 1 study [1]. Dividing each component of the contact matrix **C** by the eigenvalue $\rho(\mathbf{C})$, the normalized contact matrix is obtained, and furthermore, the matrix is multiplied by the effective reproduction number R_t, the average number of secondary infections generated by a single primary case. In our simulation, we assume the relative susceptibility of individuals vaccinated with a single or double dose of COVID-19 vaccine, denoted by v_s or v_d, is 0.35 or 0.05, respectively (i.e., 65% or 95% protection from SARS-CoV-2 infection upon exposure). The proportion individuals in an age subgroup i that has taken one or two doses of COVID-19 vaccine are denoted by φ_i or θ_i, respectively. The resulting relative susceptibility of each age subgroup i, as denoted by σ_i, can be calculated by

$$\sigma_i = -(1 - \phi_i - \theta_i) + \big(v_s + (1 - v_s)(1 - w_i)\big)\phi_i + \big(v_d + (1 - v_d)(1 - w_i)\big)\theta_i, \tag{1}$$

where w_i is age-dependent relative vaccine efficacy, which is set as 1 (full vaccine efficacy) if the individual is younger than 60 years old, as 0.8333 if the individual is in the age interval [60, 69] years old, and as 0.6667 if the individual is older than 70 years old (Table 1).

Letting $S_i(t)$, $I_i(t)$, and $R_i(t)$, respectively, be the susceptible, infectious, and recovered population size of age group i at calendar time t, we set differential equations as follows:

$$\begin{aligned} \frac{dS_i(t)}{dt} &= -\frac{\gamma R_t \sigma_i S_i(t)}{\rho(\mathbf{C}) N_i} \sum_{j=1}^{15} C_{ij} I_j(t), \\ \frac{dI_i(t)}{dt} &= \frac{\gamma R_t \sigma_i S_i(t)}{\rho(\mathbf{C}) N_i} \sum_{j=1}^{15} C_{ij} I_j(t) - \gamma I_i(\mathrm{t}), \\ \frac{dR_i(t)}{dt} &= \gamma I_i(t), \end{aligned} \tag{2}$$

where γ is the rate of recovery from COVID-19 per unit of time, which in this study is assumed to take a constant value of 1/5 days (Table 1). That is, the duration of infectious period, τ, is assumed to be described by an exponential distribution, $f(\tau)$= $\exp(-\tau/\gamma)/\gamma$. N_i is the total population size of age group i (i.e., $N_i = S_i(t) + I_i(t) + R_i(t)$). The effective reproduction number $R(t)$ was defined as

$$R(t) := \rho\left(\frac{R_t \sigma_i S_i(t) C_{ij}}{\rho(\mathbf{C}) N_i}\right) = R_t. \tag{3}$$

Midpoint of empirically reported basic reproduction number of COVID-19 has been 2.5, and when PHSMs were in place, it was assumed that 56% decrease in the reproduction number is attained, and thus, R_t at 1.1 [24,25, 26-30]. The initial size of infectious and recovered populations in each age group (i.e., $I_i(0)$ and $R_i(0)$) were retrieved from the actual epidemiological data, i.e., empirical sum of the daily incidence from May 8–12, 2021 and cumulative number of confirmed SARS-CoV-2 infections by May 12, 2021 (see Supplementary Table S1). We set $t = 0$ as the calendar time at which the COVID-19 vaccination among older adults began. The parameters used in the equations are described in Table 1. We used Berkeley Madonna, version 10.2.8 (Robert Macey and George Oster, CA, USA), for solving the differential equations.

Table 1. Parameter values used for calculating the cumulative risks of SARS-CoV-2 infection and death from COVID-19.

Parameter	Value(s)	Reference
Effective reproduction number (R_t)	1.1 and 2.5	Assumed with reference to [24,25, 26–30]
Mean duration of infectious period in days ($1/\gamma$)	5	[51]
Relative susceptibility after one dose of vaccination (v_s)	35%	Assumed with reference to [22,52]
Relative susceptibility after two doses of vaccination (v_d)	5%	[52]
Age-dependent relative vaccine efficacy in 60-64 (w_{60}), 65-69 (w_{65}), and 70- (w_{70})	83.33%, 83.33%, and 66.67%	[6]

Table 2. Calculated cumulative numbers of SARS-CoV-2 infections and deaths with various combinations of COVID-19 vaccination strategies and PHSM.

Vaccination strategy	Duration of PHSM (during vaccination steps)	Cumulative number of infection	Death toll
A	(i) and (ii)	4,682,995	39,405
B	(i)	69,856,699	695,295
A	(i), (ii), (iii), and (iv)	1,387,078	15,442
B	(i) and (ii)	1,900,172	17,423

3. Results

For the application of COVID-19 vaccination strategy A, a total of 4,682,995 COVID-19 cases, affecting 2,563,407 children, 1,617,240 young adults, and 502,348 older adults, eventually occurred, resulting in a total of 39,405 deaths from COVID-19. The number of infectious individuals among the population of young adults peak on day 40 of the COVID-19 vaccination strategy, four days after the end of step (i) (Figure 2A). The number of infectious individuals then decreased until step (ii) was complete on day 105 of the vaccination strategy, when PHSM were lifted and the effective reproduction number was elevated from 1.1 to 2.5. The number of infectious young adults then increased again until it reached another peak on day 176 of the vaccination strategy, in the middle of step (iv).

When COVID-19 vaccination strategy B was applied instead, a total of 69,856,699 COVID-19 cases, affecting 16,505,999 children, 45,264,967 young adults, and 8,085,733 older adults, eventually occurred, resulting in a total of 695,295 deaths from COVID-19 (Figure 2B). The numbers of infectious individuals among the young adult and older adult populations became extremely large when step (i) was complete and the PHSM were lifted on day 68 of the COVID-19 vaccination strategy. The size of the infected population decreased thereafter.

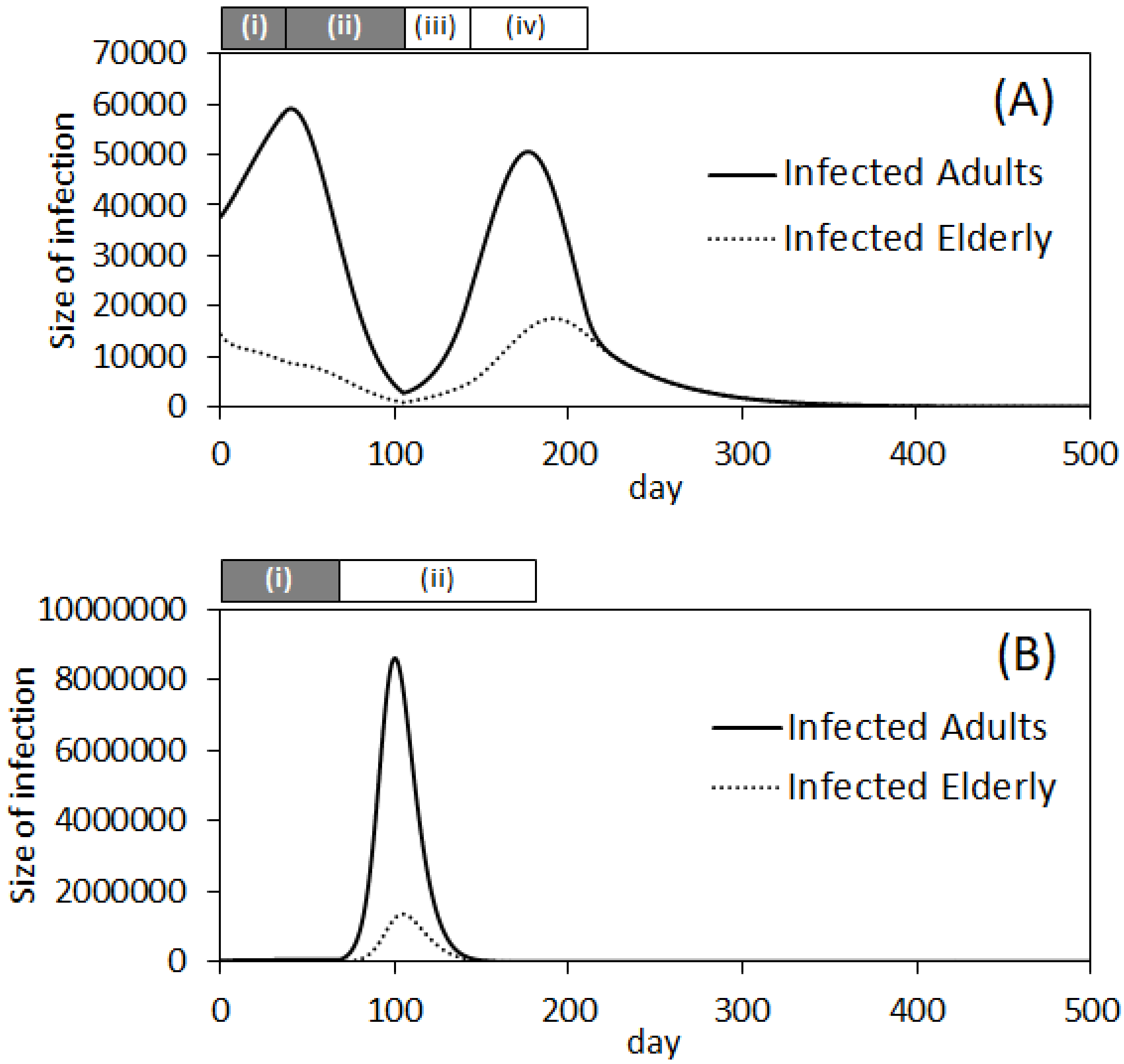

Figure 2. Epidemic curve in two vaccine strategies with limited PHSM duration. Infectious individuals among the young adult and older adult populations (A) when vaccine rollout strategy A was implemented in combination with the application of PHSM during steps (i) and (ii), and (B) when vaccine rollout strategy B was implemented in combination with the application of PHSM during step (i).

Assuming that PHSM were continued through the time when 100% of double-dose COVID-19 vaccination is achieved among both young and older adults, the application of strategy A yielded a cumulative number of 1,387,078 COVID-19 cases, affecting 263,315 children, 928,518 young adults, and 195,245 older adults (Figure 3A), in which the relative risks of SARS-CoV-2 infection and death from COVID-19 were 29.6% and 39.4%, respectively, compared with the application of strategy A with PHSM of limited duration (Figure 2A).

For the application of strategy B with an extended period of PHSM, there would be a total of 1,900,172 COVID-19 cases, affecting 377,107 children, 1,315,927 young adults, and 207,138 older adults (Figure 3B); these figures are only 2.7% of those predicted for the application of this vaccination strategy with PHSM of limited duration (Figure 2B). This alternate plan would lead to a total death toll from COVID-19 of 17,423 persons, which is only 2.5% of that predicted for the use of strategy B with PHSM of limited duration (Figure 2B).

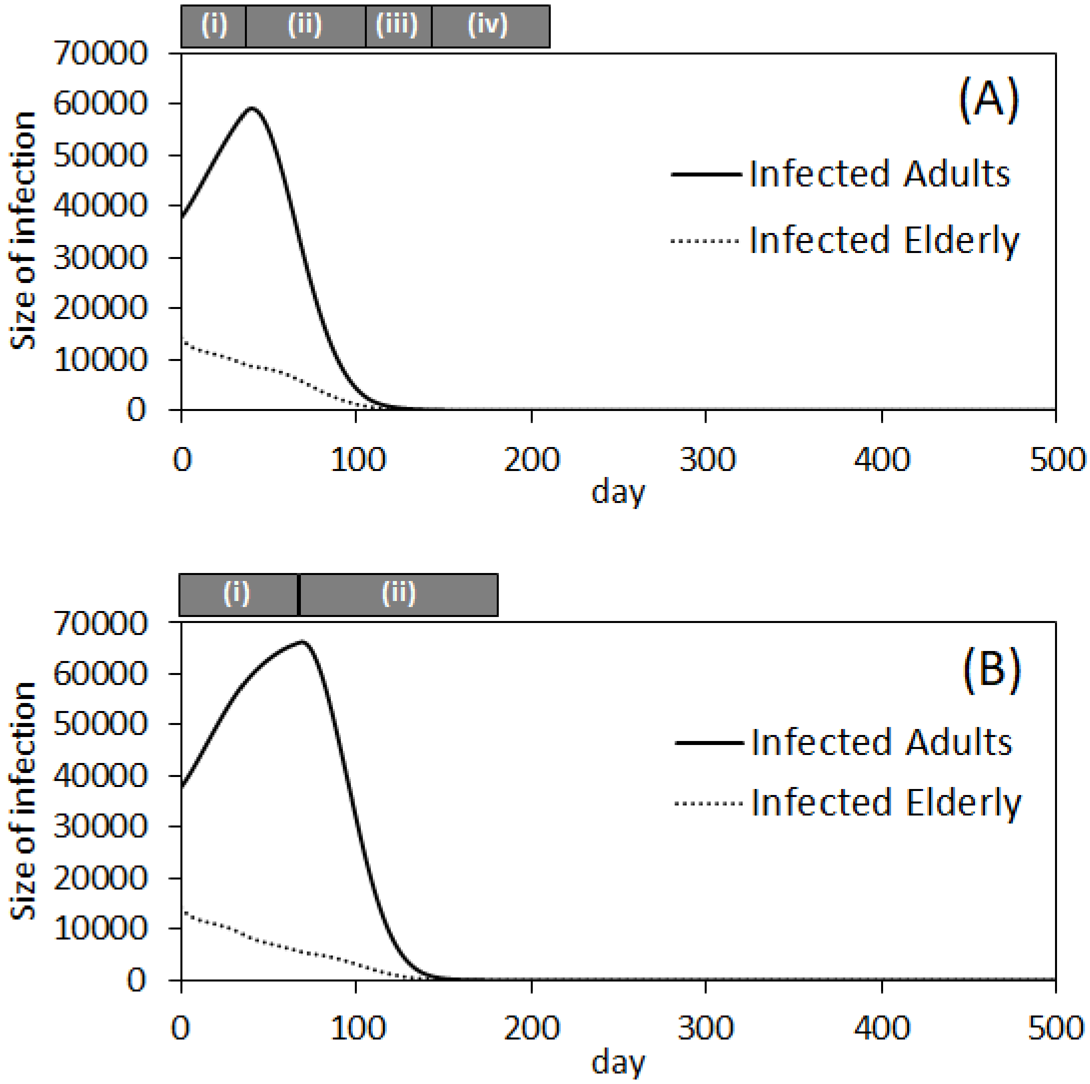

Figure 3. Epidemic curve in two prioritization strategies under public health and social measures (PHSM) for the entire period of time. Numbers of infectious individuals among young and older adults. (A) When COVID-19 vaccine rollout strategy A was implemented in combination with PHSM for the entire period of time, and (B) when vaccine rollout strategy B was implemented with an extended period of PHSM.

4. Discussion

The present study investigated the age-dependent transmission dynamics of COVID-19, comparing two different policies in prioritizing COVID-19 vaccination, i.e., single- vs double-dose. Given a fixed realistic value of the rate at which susceptible individuals will receive a dose of COVID-19 vaccine (i.e., 1 million persons per day), the dynamic model revealed that taking the single-dose

COVID-19 vaccination strategy would lead to lower cumulative risks of SARS-CoV-2 infection and death from COVID-19 compared with implementing the double-dose vaccination strategy. Of note, combining COVID-19 vaccination and PHSM was considered to be essential, and extending the PHSM for the entire period of COVID-19 vaccination was deemed critical to avoid excessive numbers of COVID-19 cases and deaths.

There are two important take-home messages from the present study. First, expediting single-dose COVID-19 vaccination both among young and older adults, while temporarily delaying the second dose of COVID-19 vaccine, helped to minimize the risks of both SARS-CoV-2 infection and death from COVID-19. Several published studies, including our Part 1 study, showed that prioritizing COVID-19 vaccinations for older adults aged over 60 years will more efficiently reduce COVID-19 mortality and years of life lost compared with other COVID-19 vaccination strategies because of the high IFR for COVID-19 among older adults [5,6]; thus, the present study results may be regarded as counterintuitive. What we have seen as the difference between our Part 1 and Part 2 studies is that the parameter settings were static in the Part 1 study, so that the final size equation can be used, whereas the Part 2 study allowed not only parameters but also even SIR states to dynamically vary over the course of time. The reason why the Part 2 study indicated the single-dose COVID-19 vaccination strategy as more efficient, in contrast to the findings of the Part 1 study can be explained as follows: (i) the COVID-19 epidemic was growing over the course of time, and there was a competition between COVID-19 vaccination and spread of SARS-CoV-2 infection, (ii) single-dose COVID-19 vaccination helps to strengthen indirect protection, while double-dose COVID-19 vaccination is intended to ensure the protection of vulnerable people from death, and (iii) given the realistic rollout rate of COVID-19 vaccination in Japan in comparison with the assumed reproduction number of COVID-19, the disease transmission blocking option, i.e., single-dose vaccination strategy, was favored to reduce the risks of SARS-CoV-2 infection and death from COVID-19. However, the difference in the expected number of deaths from COVID-19 in the presence of PHSM was less than 2000. Whether to delay the second dose of COVID-19 vaccination in a situation with a limited supply of COVID-19 vaccine was discussed previously [31-33]. While a published simulation study found that the delay of a second dose of COVID-19 vaccine may not contribute to a clear advantage unless the efficacy of the first dose of COVID-19 vaccine does not wane at all over time [34], our model with specific parameters for Japan showed that delaying the second dose of COVID-19 was slightly beneficial.

Second, it must be noted that vaccination alone was insufficient to suppress the COVID-19 epidemic in Japan, even provided that vaccinating one million persons per day was achieved. PHSM were necessary to minimize the size of the SARS-CoV-2-infected population and the death toll from COVID-19 until the nation gained substantial protection from herd immunity [15,35-39]. In Figure 2, earlier wave started to decrease due mainly to PHSM, while second wave (later wave) declined due to increased coverage of vaccination. It should be noted that our Part 1 study, which indicated that the double-dose COVID-19 vaccination strategy would be favored, did not account for PHSM at all and must have had to assume that COVID-19 vaccination was complete by the beginning of an epidemic. What we have since learnt from more realistic modeling is that combining pharmaceutical and non-pharmaceutical approaches will be deemed vital for avoiding tragic COVID-19 epidemic outcomes.

As of June 17, 2021, the speed of the COVID-19 vaccine rollout was limited in Japan; only 600,000 doses per day, at most, were administered [40]. Nonetheless, Japan faced a dilemma about whether to host the Tokyo Olympic Games beginning in late July, while the Delta variant of SARS-CoV-2 was certainly replacing the less transmissible Alpha variant of SARS-CoV-2 [41-48]. The public opinion that hosting the Olympic Games was not realistic gradually grew when the daily incidence of COVID-19 was reported to be 1,500 cases, even in the middle of a state of emergency being declared in nine prefectures, including four metropolitan cities [49]. The application of more intense social interventions, such as a lockdown, was argued to be required. The COVID-19 vaccination rollout was then politically accelerated to achieve the completion of at least partial protection from COVID-19 before the beginning of the Tokyo Olympic Games, aiming to offer double-dose COVID-19 vaccination among older adults by that time. Besides, as we have shown here, a COVID-19 vaccination rollout alone appeared not to be sufficient to halt the transmission of COVID-19, and this was particularly relevant in light of the time delay between COVID-19 vaccination and subsequent protection via herd immunity [15,35].

There are several limitations in this study. First, as we performed the modeling analysis, we did not consider the time gap between receiving COVID-19 vaccination and achieving the SARS-CoV-2-specific antibody titers necessary to reach a protective level [50]. Ideally, allowing a time delay of approximately 14 days to build up immune protection in each vaccinated individual would have led to more realistic simulations. Second, the death toll from COVID-19 was simply calculated as the product of the final size of the SARS-CoV-2-infected population and the age-specific IFR. This is considered as a limitation because the number of individuals who died should have been removed from the population, potentially yielding a greater number of COVID-19 cases than what we have shown here. Third, for simplicity, the impact of having a SARS-CoV-2 variant of concern was not explicitly taken into account, while in reality the Alpha and Delta variants of SARS-CoV-2 were the dominant strains shortly before the Tokyo Olympic Games [26]. Fourth, the effective reproduction number was fixed at a value of 1.1 during the implementation of PHSM and at a value of 2.5 otherwise [24,25] in a simple manner. If the reproduction number was far more elevated, the double-dose vaccination strategy could have been superior to the single-dose vaccination strategy. Nonetheless, we believe that our simulation at least offers a theoretical approach to determining the preferred COVID-19 vaccination strategy that could minimize the cumulative risks of SARS-CoV-2 infection and death from COVID-19.

5. Conclusions

While static modelling (e.g. the model with static parameters that used final size equation) suggested double dose as optimal, interestingly, real-time investigation favored the disease transmission blocking option, i.e., single-dose vaccination strategy. Expediting single-dose COVID-19 vaccination among young and older adults would yield smaller risks of SARS-CoV-2 infection and death from COVID-19. During the COVID-19 vaccine rollout, combining PHSM with vaccination was considered to be essential, especially by the time the second dose of COVID-19 vaccine is delivered to both young and older adults. Applying the single-dose-first strategy should yield a smaller epidemic size than applying the double-dose strategy; however, for both strategies, PHSM will be essential by the time second-dose COVID-19 vaccination is complete among all adults.

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Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

1. T. Kobayashi, H. Nishiura, Prioritizing COVID-19 vaccination. Part 1: Final size comparison between a single dose and double dose, *Math. Biosci. Eng.*, **19** (2022), 7374–7387. https://doi.org/10.3934/mbe.2022348
2. J. Wood, J. McCaw, N. Becker, T. Nolan, C. R. MacIntyre, Optimal dosing and dynamic distribution of vaccines in an influenza pandemic, *Am. J. Epidemiol.*, **169** (2009), 1517–1524. https://doi.org/10.1093/aje/kwp072
3. S. Riley, J. T. Wu, G. M. Leung, Optimizing the dose of pre-pandemic influenza vaccines to reduce the infection attack rate, *PLoS Med.*, **4** (2007), e218. https://doi.org/10.1371/journal.pmed.0040218
4. H. Nishiura, K. Iwata, A simple mathematical approach to deciding the dosage of vaccine against pandemic H1N1 influenza, *Euro. Surveill.*, **14** (2009), 1–5. https://doi.org/10.2807/ese.14.45.19396-en
5. A. Levin, W. Hanage, N. Owusu-Boaitey, K. Cochran, S. Walsh, G. Meyerowitz-Katz, Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications, *Eur. J. Epidemiol.*, **35** (2020), 1123–1138. https://doi.org/10.1007/s10654-020-00698-1
6. K. Bubar, K. Reinholt, S. Kissler, M. Lipsitch, S. Cobey, Y. Grad, et al., Model-informed COVID-19 vaccine prioritization strategies by age and serostatus, *Science*, **371** (2021), 916–921. https://doi.org/10.1126/science.abe6959
7. E. Rumpler, M. J. Feldman, M. T. Bassett, M. Lipsitch, Equitable COVID-19 vaccine prioritization: front-line workers or 65–74 year olds?, preprint, Available from: https://www.medrxiv.org/content/10.1101/2022.02.03.22270414v1.full
8. G. Persad, E. J. Emanuel, S. Sangenito, A. Glickman, S. Phillips, E. A. Largent, Public perspectives on COVID-19 vaccine prioritization, *JAMA Netw. Open*, **4** (2021), e217943. https://doi.org/10.1001/jamanetworkopen.2021.7943
9. G. Persad, M. E. Peek, E. J. Emanuel, Fairly prioritizing groups for access to COVID-19 vaccines, *JAMA*, **324** (2020), 1601–1602. https://doi.org/10.1001/jama.2020.18513
10. K. Dooling, N. McClung, M. Chamberland, M. Marin, M. Wallace, B. P. Bell, et. al., The advisory committee on immunization practices' interim recommendation for allocating initial supplies of

COVID-19 vaccine—United States, 2020, *MMWR Morbid. Mortal W.*, **69** (2020), 1857–1859. https://doi.org/10.15585/mmwr.mm6949e1
11. J. Buckner, G. Chowell, M. Springborn, Dynamic prioritization of COVID-19 vaccines when social distancing is limited for essential workers, *Proc. Natl. Acad. Sci. U. S. A.*, **118** (2021), e2025786118. https://doi.org/10.1073/pnas.2025786118
12. P. Jentsch, M. Anand, C. Bauch, Prioritising COVID-19 vaccination in changing social and epidemiological landscapes: A mathematical modelling study, *Lancet Infect. Dis.*, **3099** (2021), 00057-8. https://doi.org/10.1016/S1473-3099(21)00057-8
13. S. Han, J. Cai, J. Yang, J. Zhang, Q. Wu, W. Zheng, et al., Time-varying optimization of COVID-19 vaccine prioritization in the context of limited vaccination capacity, *Nat. Commun.*, **12** (2021), 4673. https://doi.org/10.1038/s41467-021-24872-5
14. N. Askitas, K. Tatsiramos, B. Verheyden, Estimating worldwide effects of non-pharmaceutical interventions on COVID-19 incidence and population mobility patterns using a multiple-event study, *Sci. Rep.*, **11** (2021), 1972. doi: https://doi.org/10.1038/s41598-021-81442-x
15. S. Flaxman, S. Mishra, A. Gandy, H. J. T. Unwin, T. A. Mellan, H. Coupland, et.al., Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe, *Nature*, **584** (2020), 257–261. doi: https://doi.org/10.1038/s41586-020-2405-7
16. S. Moore, E. M. Hill, M. J. Tildesley, L. Dyson, M. J. Keeling, Vaccination and non-pharmaceutical interventions for COVID-19: A mathematical modelling study, *Lancet Infect. Dis.*, **3099** (2021), 793–802. https://doi.org/10.1016/S1473-3099(21)00143-2
17. An open letter by a group of public health experts, clinicians, scientists, COVID-19: An urgent call for global "vaccines-plus" action, *BMJ*, **376** (2022), 1–3. https://doi.org/10.1136/bmj.o1
18. M. Coccia, Preparedness of countries to face COVID-19 pandemic crisis: Strategic positioning and factors supporting effective strategies of prevention of pandemic threats, *Environ. Res.*, **203** (2022), 111678. https://doi.org/10.1016/j.envres.2021.111678
19. K. Prem, Y. Liu, T. Russell, A. Kucharski, R. Eggo, N. Davies, et al., The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: A modelling study, *Lancet Public Health*, **5** (2020), e261–e270. https://doi.org/10.1016/S2468-2667(20)30073-6
20. B. Dickens, J. Koo, J. Lim, M. Park, S. Quaye, H. Sun, et al., Modelling lockdown and exit strategies for COVID-19 in Singapore, *Lancet Regional Health—Western Pacific*, **1** (2020) 100004. https://doi.org/10.1016/j.lanwpc.2020.100004
21. L. Munasinghe, Y. Asai, H. Nishiura, Quantifying heterogeneous contact patterns in Japan: A social contact survey, *Theor. Biol. Med. Model.*, **16** (2019), 6. https://doi.org/10.1186/s12976-019-0102-8
22. E. Mahase, Covid-19: Reports from Israel suggest one dose of Pfizer vaccine could be less effective than expected, *BMJ*, **372** (2021), n217. https://doi.org/10.1136/bmj.n217
23. H. Nishiura, Tracking public health and social measures, in World Health Organization, 2021, work in progress.
24. T. Kuniya, Evaluation of the effect of the state of emergency for the first wave of COVID-19 in Japan, *Infect. Dis. Model.*, **5** (2020), 580–587. https://doi.org/10.1016/j.idm.2020.08.004
25. K. Nakajo, H. Nishiura, Assessing interventions against Coronavirus Disease 2019 (COVID-19) in Osaka, Japan: A modeling study, *J Clin. Med.*, **19** (2021), 1256. https://doi.org/10.3390/jcm10061256

26. *Ministry of Health, Labor and Welfare*: COVID-19 Advisory Board, (Japanese), 2021. Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00216.html.
27. I. Locatelli, B. Trächsel, V. Rousson, Estimating the basic reproduction number for COVID-19 in Western Europe, *PLoS One*, **16** (2021), 1–9. https://doi.org/10.1001/jama.2021.3341
28. Z. Zhuang, S. Zhao, Q. Lin, P. Cao, Y. Lou, L. Yang, et al., Preliminary estimates of the reproduction number of the coronavirus disease (COVID-19) outbreak in Republic of Korea and Italy by 5 March 2020, *Int. J. Infect. Dis.*, **95** (2020), 308–310. https://doi.org/10.1016/j.ijid.2020.04.044
29. M. Al-Raeei, The basic reproduction number of the new coronavirus pandemic with mortality for India, the Syrian Arab Republic, the United States, Yemen, China, France, Nigeria and Russia with different rate of cases, *Clin. Epidemiol. Glob. Heal.*, **9** (2021), 147–149. https://doi.org/10.1016/j.cegh.2020.08.005
30. M. A. Billah, M. M. Miah, M. N. Khan, Reproductive number of coronavirus: A systematic review and meta-analysis based on global level evidence, *PLoS One*, **15** (2020), e0242128. https://doi.org/10.1371/journal.pone.0242128
31. E. Mahase, COVID-19: Order to reschedule and delay second vaccine dose is "totally unfair," says BMA, *BMJ*, **371** (2020), m4978. https://doi.org/10.1136/bmj.m4978
32. S. Kadire, R. Wachter, N. Lurie. Clinical decisions delayed second dose versus standard regimen for COVID-19 vaccination: A task force on administration of COVID-19 vaccine recommend delaying the second dose recommend following the standard Regimen, *N. Engl. J. Med.*, **384** (2021), e28. https://doi.org/10.1056/NEJMclde2101987
33. G. Iacobucci, G. E. Mahase, COVID-19 vaccination: What's the evidence for extending the dosing interval? *BMJ*, **372** (2021), n18. https://doi.org/10.1136/bmj.n18
34. S. Moghadas, T. Vilches, K. Zhang, S. Nourbakhsh, P. Sah, M. Fitzpatrick, et al., Evaluation of COVID-19 vaccination strategies with a delayed second dose, *PLoS Biol.*, **19** (2021), 1–13. http://dx.doi.org/10.1371/journal.pbio.3001211
35. K. Leung, M. Jit, G. M. Leung, J. T. Wu, The allocation of COVID-19 vaccines and antivirals against emerging SARS-CoV-2 variants of concern in East Asia and Pacific region: A modelling study, *Lancet Regional Health — Western Pacific*, **21** (2022), 100389. https://doi.org/10.1016/j.lanwpc.2022.100389
36. L. Tian, X. Li, F. Qi, Q. Tang, V. Tang, J. Liu, et al., Harnessing peak transmission around symptom onset for non-pharmaceutical intervention and containment of the COVID-19 pandemic, *Nat. Commun.*, **12** (2021), 1147. https://doi.org/10.1038/s41467-021-21385-z
37. M. Coccia, Optimal levels of vaccination to reduce COVID-19 infected individuals and deaths: A global analysis, *Environ. Res.*, **204** (2022), 112314. doi: https://doi.org/10.1016/j.envres.2021.112314
38. L. S. F. Frederiksen, Y. Zhang, C. Foged, A. Thakur, The long road toward COVID-19 herd immunity: Vaccine platform technologies and mass immunization strategies, *Front. Immunol.*, **11** (2020), 1817. https://doi.org/10.3389/fimmu.2020.01817
39. K. O. Kwok, F. Lai, W. I. Wei, S. Y. S Wong, J. W. T. Tang, Herd immunity - estimating the level required to halt the COVID-19 epidemics in affected countries, *J. Infect.*, **80** (2020), e32–e33. doi: https://doi.org/10.1016/j.jinf.2020.03.027

40. *Cabinet Public Relations Office*: Novel Coronavirus Vaccines: Total number of vaccine doses administered to date, 2021. Available from: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html
41. E. Mahase, COVID-19: Novavax vaccine efficacy is 86% against UK variant and 60% against South African variant, *BMJ*, **372** (2021), n296. https://doi.org/10.1136/bmj.n296
42. J. Wise, COVID-19: The E484K mutation and the risks it poses, *BMJ*, **372** (2021), n359. https://doi.org/10.1136/bmj.n359
43. T. Burki, Understanding variants of SARS-CoV-2, *Lancet*, **397** (2021), 462. https://doi.org/10.1016/S0140-6736(21)00298-1
44. V. Biotechnology, S. Francisco, I. Diseases, C. L. Moncucco, L. S. Hospital, A. Hospital, et al., SARS-CoV-2 B.1.1.7 sensitivity to mRNA vaccine-elicited, convalescent and monoclonal antibodies, preprint, Available from https://www.medrxiv.org/content/10.1101/2021.01.19.21249840v4
45. D. Planas, T. Bruel, L. Grzelak, F. Guivel-Benhassine, I. Staropoli, F. Porrot, et al., Sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to neutralizing antibodies, *Nat. Med.*, **27** (2021), 917–924. https://doi.org/10.1038/s41591-021-01318-5
46. A. Muik, A. K. Wallisch, B. Sänger, K. A. Swanson, J. Mühl, W. Chen, et al., Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine–elicited human sera, *Science*, **371** (2021), 1152–1153. https://doi.org/10.1126/science.abg6105
47. P. Wang, M. S. Nair, L. Liu, S. Iketani, Y. Luo, Y. Guo, et al., Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7, *Nature*, **593** (2021), 130–135. https://doi.org/10.1038/s41586-021-03398-2
48. D. Zhou, W. Dejnirattisai, P. Supasa, C. Liu, A. J. Mentzer, H. M. Ginn, et al., Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera, *Cell*, **184** (2021), 2348–2361. https://doi.org/10.1016/j.cell.2021.02.037
49. *The Center for Systems Science and Engineering (CSSE) at Johns Hopkins University*: COVID-19 Dashboard, 2021. Available from: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6
50. S. Saadat, Z. R. Tehrani, J. Logue, M. Newman, M. B. Frieman, A. D. Harris, et al., Binding and neutralization antibody titers after a single vaccine dose in health care workers previously infected with SARS-CoV-2, *JAMA*, **325** (2021), 1467–1469. https://doi.org/10.1001/jama.2021.3341
51. N. G. Davies, A. J. Kucharski, R. M. Eggo, A. Gimma, W. J. Edmunds, T. Jombart, et al., Effects of non-pharmaceutical interventions on COVID-19 cases, deaths, and demand for hospital services in the UK: A modelling study, *Lancet Public Health*, **5** (2020), e375–e785. https://doi.org/10.1016/S2468-2667(20)30133-X
52. N. Dagan, N. Barda, E. Kepten, O. Miron, S. Perchik, M. A. Katz, et al., BNT162b2 mRNA COVID-19 vaccine in a nationwide mass vaccination setting, *N. Engl. J. Med.*, **384** (2021), 1412–1423. https://doi.org/10.1056/NEJMoa2101765
53. *Toyo Keizai Online COVID-19 Task Team*: Coronavirus Disease (COVID-19) Situation Report in Japan. Toyo Keizai Online, 2021. Available from: https://toyokeizai.net/sp/visual/tko/covid19/en.html

Supplementary

Supplementary Table 1. Initial values of infectious and recovered individuals.

Age group	Initial size of infected population of age i, $I_i(0)$	Initial size of recovered population of age i, $R_i(0)$
0–4 (i = 1)	966	2960.5
5–9 (i = 2)	966	2960.5
10–14 (i = 3)	2035.5	7603
15–20 (i = 4)	2035.5	7603
21–24 (i = 5)	5548	29173
25–29 (i = 6)	5548	29173
30–34 (i = 7)	3794	19716
35–39 (i = 8)	3794	19716
40–44 (i =9)	4183.5	18367.5
45–49 (i = 10)	4183.5	18367.5
50–54 (i = 11)	3924	16672
55–59 (i = 12)	3924	16672
60–64 (i = 13)	2857.5	10714
65–69 (i =14)	2857.5	10714
70– (i =15)	11464	35864

Ri(0) was derived from the cumulative number of confirmed COVID-19 cases. As the empirical data [53] were described for 10-year age groups, we rearranged those values into 5-year age groups by dividing the observed value by 2. Ii(0) was calculated as the sum of observed daily COVID-19 incidence for 5 days, taking the sum from May 8–12, 2021. We ignored under-ascertainment of COVID-19 cases for the determination of those initial values.