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Optimizing COVID-19 vaccination programs during vaccine shortages

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ABSTRACT

During the ongoing COVID-19 pandemic, vaccine shortages occur due to various types of constraints, including interruptions in production/supply, higher-than-expected demands, and a lack of resources such as healthcare capacity to administer vaccines. Scientifically informed epidemic models have been utilized as pivotal tools to optimize the immunization programs subject to vaccine shortages. The current paper reviews modelling methods to optimize the allocation strategies of vaccines with differential efficacies by using various model-based outcome measures. The models reviewed in this study are expected to be adopted and extended to make contributions on policy development for disease control under the vaccine shortage scenario.

1. Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused an unprecedented pandemic of coronavirus disease 2019 (COVID-19) in a very short time due to its high transmissibility (Hu et al., 2021; Leung et al., 2020). Before curative treatment drugs or vaccines are available, most countries implement a series of non-pharmaceutical interventions (NPIs) including wearing masks, testing and tracing suspected cases, social distancing and even locking down COVID-19 epidemic centers (Lai et al., 2020; Liu et al., 2021c). Although these NPIs have appeared to be effective in mitigating the initial wave of COVID-19, continually emerged COVID-19 cases lead to subsequent waves once there is a relaxation of these NPIs (Kissler et al., 2020). In addition to that, these NPIs have enormously affected social and economic costs (ECDC, 2020a). Safe and effective vaccines against COVID-19 are urgently needed, which were widely expected to help acquire adequate herd immunity and bring the COVID-19 pandemic to an end (Fontanet & Cauchemez, 2020; Jeyanathan et al., 2020).

The development of COVID-19 vaccines exhibited extraordinary fast speed. Within less than one year, several pharmaceutical companies successfully developed various types of vaccines against COVID-19. As of November 2021, the COVID-19 vaccine tracker shows that among 160 vaccine candidates, 24 vaccines have been approved and granted emergency use authorization by at least one country and 8 vaccines have been approved for emergency use by the World Health Organization (WHO) (Vaccine Tracker, 2021). Even though more licensed vaccines become available, many countries especially low-income countries are still confronted with the scarcity of COVID-19 vaccine supply, which pose challenges in achieving WHO's goal of

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20% vaccination coverage for each country by the end of 2021 (Ritchie et al., 2020; WHO, 2021c, 2021d). Furthermore, the newly identified coronavirus variants, including the latest variant Omicron (B.1.1.529) reported to WHO from South Africa on November 24, 2021 (WHO, 2021e), bring concerns on dropped efficacy of existing vaccines and demands for urgent development of variant-specific COVID vaccines for booster shots. However, it takes time to mass-produce these variant-specific vaccines and the safe and efficient distribution is also hindered by other logistical constraints. Shortage of healthcare capacity to administer vaccines and other resources pose additional challenges on immunization programs to reduce the negative impact of the COVID-19 pandemic. Under these shortage scenarios, it is imperative to implement judicious vaccination strategies for most countries.

Based on the vision of equitable distribution of COVID-19 vaccines, many public health authorities have put forward some provisional guidance documents of feasible vaccination actions for local governments (CDC, 2020; ECDC, 2021; WHO, 2021c). According to WHO's guidance on phased global vaccination strategy, three options corresponding to different ambition levels of vaccination are recommended (WHO, 2021c): (a) the 'universal global vaccination strategy' aiming to completely control the pandemic by vaccinating all populations, which would be too ambitious to realize for most countries in the current situation; and (b) other two priority strategies with lower level of ambition focusing on vaccinating all adult (30+ year) and older adult (50+ year) population respectively. The less ambitious strategies, aiming at alleviating the disease burden on socio-economic activity and health systems, are more realistic for the current situation and recommended by most health authorities as well (ECDC, 2020b; NASEM, 2020; The state council information office, P.R. China, 2020). Furthermore, the Strategic Advisory Group of Experts on Immunization (SAGE) has published several interim guidance statements for prioritizing use of COVID-19 vaccines in the context of constrained supply and logistical constraints (WHO, 2021). Beyond the traditional priority strategies mentioned above to minimize the adverse effects due to vaccine shortage, the scarcity of COVID-19 vaccines forced several countries to implement other exceptional vaccination strategy, including dose-stretching strategy by postponing the second dose to increase the vaccine coverage of first dose (DHSC, 2021). In addition, WHO has recently proposed an interim statement about recommendation of another alternative dose-sparing vaccination strategy to cope with global vaccine shortage, that is, fractionalizing one dose into several fractional doses to vaccinate more people (WHO, 2021b).

Even though there are general guidances recommended by international and national health officials, local policy makers may still concern detailed region-specific issues involved in the rollout of specific vaccination strategies, such as fair setting of proper targeted/priority order, rational delayed period between two doses, the selection of effective fractional dose and the impact on controlling COVID-19 amidst/post vaccination (Pimenta et al., 2021; Więcek et al., 2021; Yang et al., 2021b). In particular, a matter of public concern is whether vaccination alone can defeat COVID-19 while easing NPIs completely (Huang et al., 2021). It has been proved that mathematical models can not only characterize different transmission scenarios but also provide important scientific evidences for decision making in the course of combating COVID-19 (McBryde et al., 2020; Panovska-Griffiths, 2020). A wide variety of modelling frameworks have been proposed to assess the population-level influence of various intervention strategies (Meehan et al., 2020; Padmanabhan et al., 2021). Along with the development of COVID-19 vaccines, quite a few studies explored optimal vaccination distribution issues by utilizing mathematical models (Li et al., 2020; Makhoul et al., 2020; Olivares & Staffetti, 2021). The current manuscript is to provide a brief overview of model-based effectiveness analyses of existing COVID-19 vaccination strategies (priority vaccination, delaying the second dose, and dose sparing by utilizing fractional doses) in the context of limited vaccine supply. Not only low-income countries struggling to vaccinate their populations, but also richer nations facing the shortage of possible variant-specific booster shots, can propose judicious policies on vaccination distribution to optimize the control efficacy with the aid of mathematical models. The public health community may also get prepared for a future pandemic in the case of vaccine shortage.

2. Basic setting

We conducted a literature review on Web of Science with various combinations of the following key words: 'COVID-19 OR SARS-CoV-2' and '(optimal) vaccination strategy OR programs' and 'limited OR shortage' and 'mathematical OR compartmental models' to identify published papers. The inclusion criteria are that selected work should use mathematical models as the main tool to investigate population-level impacts of COVID-19 vaccination strategy under a shortage scenario. After reviewing 39 searched results, 12 publications related to model-based investigations of vaccination programs are included based on these criteria. Then, we searched on Google Scholar in the same way and found 4 additional relevant preprints. In total, 16 modelling studies assessing vaccination impacts on COVID-19 were reviewed in detail. The majority of identified papers adopt deterministic compartment models to describe the virus transmission and vaccine efficacy. According to the evolutionary characteristics of COVID-19, classical susceptible-exposed-infectious-recovered (SEIR) model can be extended to include more detailed classifications of infected and clinical compartments. After getting infected and moving to the exposed compartment, individuals would become pre-symptomatically infectious. The pre-symptomatically infectious individuals would develop into either asymptomatically or symptomatically infectious. Based on the symptomatic severity, the infectious individuals with either severe or mild syndromes will be isolated/quarantined in hospitals. Infectious individuals will either recover or die. In order to model the impact of vaccination, additional vaccinated compartments can be added. Furthermore, various factors affecting the effectiveness of vaccination programs can be integrated into the modelling framework. These factors contain intrinsic characteristics of vaccine (including vaccine efficacy and vaccine-induced immunity), and extrinsic factors such as the transmissibility of virus, vaccine allocation modes, targeted immunization coverage, vaccine hesitancy and the strength of NPIs. We will start by introducing a basic compartmental structure in the next section and summarizing the

main model-based epidemiological indices before demonstrating various modelling frameworks under various vaccination strategies.

2.1. A basic compartmental model and model-based indices

The collection of modelling studies to optimize the vaccination programs is expanding, and these models are formulated based on questions of interest and underlying assumptions by taking a balance between the model complexity and model performance in public health. To highlight the modelling idea on vaccine shortage, it is attractive to illustrate the modelling extensions with a basic compartmental structure.

The basic model, with compartmental structure in Fig. 1, is formulated after weighing epidemiological model performances against model complexity. SARS-CoV-2 can be spread by infected individuals who never develop symptoms (asymptomatic transmission), people who are infected but have not developed symptoms yet (pre-symptomatic transmission), as well as persons who have symptoms (Ferretti et al., 2020; WHO, 2021e). It is important to distinguish three transmission routes for better evaluating the transmission risk and developing public health strategies to contain transmission. In this model, individuals are classified into different groups based on the infection and vaccination states as susceptible, exposed, asymptomatic, presymptomatic, symptomatic, removed, and fully-protected vaccinated classes (denoted with "SEAPIRV" respectively in the variables). Similar compartmental structures have been employed in existing studies to quantify the virus transmission (Ferretti et al., 2020), to simulate the phase transitions and control measures in an epidemic network (Braun et al., 2020; Patel et al., 2021), to evaluate the impact of isolation (Yang et al., 2021a), to quantify asymptomatic infection with testing capacity (Subramanian, He, & Pascual, 2021), to assess the efficiency of control strategies (such as school closures, mobility restrictions and social distancing) (Giordano et al., 2021; Moore et al., 2021b; Radulescu, Williams, & Cavanagh, 2020), and to investigate the joint effect of reopening and other control measures in the COVID-19 control (Zu et al., 2021). The dynamics of population sizes in these compartments can be described by a set of differential equations through rates of change, with the diagram shown in Fig. 1:

$$\begin{cases} \dfrac{dS(t)}{dt} = -\lambda(t)S(t) & \text{susceptible} \\ \dfrac{dE(t)}{dt} = \lambda(t)S(t) - \gamma_E E(t) & \text{latent} \\ \dfrac{dA(t)}{dt} = \rho_A \gamma_E V_E(t) - \gamma_A A(t) & \text{asymptomatic and infectious} \\ \dfrac{dP(t)}{dt} = (1-\rho_A)\gamma_E E(t) - \gamma_P P(t) & \text{presymptomatic and infectious} \\ \dfrac{dI(t)}{dt} = \gamma_P P(t) - \gamma_I I(t) & \text{symptomatic and infectious} \\ \dfrac{dR(t)}{dt} = \gamma_A A(t) + \gamma_I I(t) & \text{treated and recovered individuals} \\ V(t) \equiv V(0) = \rho_V N & \text{vaccinated with full protection} \end{cases} \tag{1}$$

In this system, γ_j for $j = E, P, I, A$ denote the transition rates from the compartment j, ρ_V represents the proportion of vaccinated individuals and ρ_A is the proportion of exposed individuals moving to the asymptomatic class. The force of infection $\lambda(t)$ (i.e., the per-susceptible rate of infection) can be expressed as

$$\lambda(t) = \frac{\beta_A A(t) + \beta_P P(t) + \beta_I I(t)}{N}.$$

Please note that in this model, for simplicity, $\rho_V = \varepsilon p_V$ by assuming that a proportion p_v of individuals are vaccinated, among whom, a proportion ε of individuals get full protection (considering the primary vaccine failure or all-or-nothingness, where a proportion of immunized individuals get full protection). For other aspects of vaccine protection and vaccine impact, we refer the readers to (Bubar et al., 2021; Magpantay, 2017). Then the numbers of doses administrated are $p_V N$ for one-dose vaccines (such as Johnson & Johnson COVID-19 vaccine) and $2p_V N$ for two-dose vaccines (such as Sinovac, Pfizer-BioNTech, Moderna and AstraZeneca COVID-19 vaccines), respectively. The parameters and values are summarized in Table 1. Although more compartmental classes are necessary to address the questions in study sometimes, for example, classes Q, D, H^m and H^S may be included in a model to represent the sizes of individuals quarantined, died from the disease, hospitalized with mild symptoms H^m and hospitalized with severe symptoms H^S, respectively. In this review, we use SEAPIRV modelling structure to serve as a benchmark to demonstrate the various modelling extensions to evaluate the efficiency of vaccination programs. Increasing evidences show that all approved COVID-19 vaccines can only provide partial protection to the vaccinated individual, and therefore, the leakiness of vaccine efficacy should be considered. For that purpose, additional compartments in Fig. 1(b) for those partially protected groups should be incorporated to system (1). To distinguish the possible

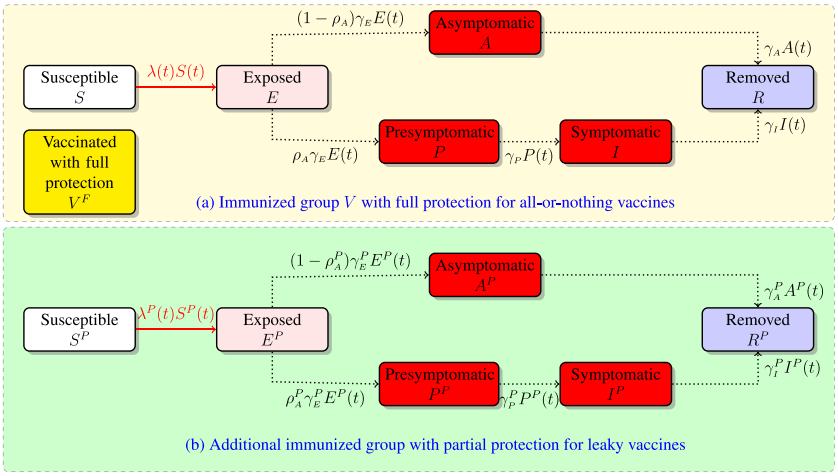

Fig. 1. (a) The diagram of the benchmark model (1) when primary failure of vaccines is considered. (b) When the efficacy of leaky vaccines is considered, more compartments, in addition to those in (a) for partially protected group should be considered.

efficacy of leaky vaccines, different parameters on infectiousness, susceptibility, incubation, recovery and infectious periods as well as the proportions should be involved (those parameters with super script P in diagram 1(b)).

2.2. Vaccine efficacy and measurements of outcomes

Various measurements of outcomes have been employed in studies to compare the impact of different vaccination strategies. Most of them can be directly projected through the model, such as (i) the reproduction number, (ii) the (daily or cumulative) number of (asymptomatic/symptomatic) infections, (iii) (daily or cumulative) number of deaths; (iv) years of life lost (YLL), which calculates the expected remaining time (i.e., time lost) for each death (Acuña-Zegarra et al., 2021; Bubar et al., 2021) and loss of quality adjusted life years (QALYs) which calculates losses due to deaths and associated with severe cases requiring hospitalization; (v) infection attack rate, which represents the fraction of individuals infected during the period of an epidemic wave. Most measurements can be inferred through related variables in the model system, for example, the daily incidence can be projected from $\lambda(t)S(t)$ in the model system (1). The number of severe or critically severe cases who need ICU admissions can be simulated and validated explicitly if a corresponding compartment is explicitly incorporated in the epidemiological model. However, some studies use implicit and indirect approaches to calculate these quantities, with the help of other epidemiological characteristics. For example, model in Han et al., 2021 does not explicitly describe the dynamics of respective compartments for symptomatic infections, hospitalized infections, ICU admissions and deaths in age group i. However, these outcomes can still be projected from the model. Take the risk of ICU admissions for age group i till day T for example, it can be represented as

$$\sum_{t=0}^{T-1} r_i^{\mathrm{ICU}}(I_i(t+1)-(1-\gamma_I)I_i(t))$$

where $I_i(t)$ is the number of infectious individuals at day t and γ_I is the recovery rate. The age-specific risk factors r_i^{ICU}, accounting the risk of requiring ICU given the infection for age group i, can be found from post-hoc analysis.

Table 1
Parameters and their values in the benchmark model (1).

Parameter	Description	Baseline value
$1/\gamma_E$	Latency period	4 days (Rădulescu et al., 2020)
ρ_A	Proportion of individuals that will never show symptoms	59%–94% (WHO, 2021a, 2021b)
$1/\gamma_A$	Infection period of asymptomatic cases	12 days (Rădulescu et al., 2020)
$1/\gamma_P$	Pre-symptomatic duration	2 days (Rădulescu et al., 2020)
$1/\gamma_I$	Waiting time between showing symptoms and getting treatment	1 day (assumed)
β_A	Effective transmission rate of asymptomatic cases	0.016–0.02 (Rădulescu et al., 2020)
β_P	Effective transmission rate of presymptomatic cases	0.96–0.12 (Rădulescu et al., 2020)
β_I	Effective transmission rate of symptomatic cases	0.08–0.1 (Rădulescu et al., 2020)
$\rho_V = \varepsilon p_v$	Proportion of individuals fully protected by vaccines	
$N(t)$	Population size	

COVID-19 vaccines demonstrate an improvement in protection against infection (vaccine reduces susceptibility, thus being effective in inhibiting viral transmission as well as protecting the individual) and prevention of transmission potential (reduced infectiousness of vaccinated individuals due to lower viral load in the upper respiratory tract), milder disease, hospitalization, as well as severe disease and death (Olliaro, Torreele, & Vaillant, 2021; WHO, 2021a). Different aspects of vaccine efficacy are incorporated in these modelling studies. Two typical modelling ideas are: (i) considering the primary vaccine failure or all-or-nothingness, where the vaccine provides perfect protection to a fraction of individuals who receive it; or (ii) exploring the leakiness, where all vaccinated individuals have reduced probability of getting infection, or when infected, vaccinated individuals may have reduced infectiousness, a decreased probabilities of developing severe diseases and deaths. Given growing COVID-19 vaccine uptake, integrated effects of waning vaccine-induced immunity and incessant new variants of SARS-CoV-2 are further modeled by incorporating the immunity waning rate and adjusting the transmission rate in some investigations (Childs et al., 2021), in particular, when vaccine schedules for multiple dose vaccines are considered (Moghadas et al., 2021; Yang et al., 2021c). Heterogeneous vaccine efficacies are also considered, for example, across different age groups (Moore et al., 2021a).

Table 2 summarizes various vaccine efficacies considered and key outcome measures used in the modelling studies.

3. Overview of model-based vaccination effectiveness analyses

This section presents various allocation strategies and related modelling methods to study the effectiveness of immunization programs. The readers can refer to Table 3 for detailed description of all universal acronyms used in the models mentioned in this section.

3.1. Priority vaccination strategy

It is widely recognized that priority/targeted vaccinations always outperform uniform vaccination when vaccine shortage occurs (Anderson & May 1991). Most countries, especially medium and low-income ones, faced challenges in determining the priority order of population groups to maximize the protective effects of limited COVID-19 vaccines (Prieto Curiel & González Ramírez, 2021; Yang et al., 2021b). COVID-19 vaccines are assumed to be distributed to some priority-use group preferentially, while the remaining vaccines would be allocated equitably regardless of priority without hesitance. Normally, essential workers including health-care and community workers are defined as high-risk groups of population who were given the highest priority to receive vaccination (WHO, 2021). The remaining population can be prioritized by many features including age, risk, geography, and so on. To describe the priority vaccination strategies, the whole population is divided into different

Table 2
Characteristics of vaccine efficacy included and key measurements used.

Study	Vaccine efficacy	Measurements
Bubar et al. (2021)	All-or-nothing vaccine & leaky vaccine (preventing infection)	Reproduction number, cumulative number of infections and death, Years of life lost due to death at a particular age
Foy et al. (2021)	All-or-nothing vaccine	Numbers of infection, symptomatic infections, cumulative death
MacIntyre, Costantino, and Trent (2021)	All-or-nothing vaccine	Daily infection, cumulative infection and deaths numbers
Choi et al. (2021b)	Leaky vaccine (preventing infection)	Cumulative confirmed cases and deaths, reproduction number
Moore et al. (2021a)	Leaky vaccine (preventing infection and symptomatic and severe disease)	Daily and accumulative deaths, quality adjusted life years (QALYs) lost
Wang et al. (2021)	Leaky vaccine (preventing infection and symptomatic disease)	Number of deaths
Barreiro et al. (2021)	All-or-nothing and loss of immunity	Daily cases
Fuady, Nuraini, Sukandar, and Lestari (2021)	All-or-nothing	Number of active cases
Lee, Li, Liu, and LeDuc (2021)	All-or-nothing vaccine & leaky vaccine	Attack rate, mortality rate, daily prevalence, total infection
Han et al. (2021)	All-or-nothing vaccine & leaky vaccine (preventing infection and disease)	Numbers of infections, symptomatic cases, hospitalizations, ICUs, and deaths
Mandal, Arinaminpathy, Bhargava, and Panda (2021)	Leaky vaccine (preventing infection and disease)	Number of deaths
Moghadas et al. (2021)	Leaky vaccine (preventing infection and symptomatic disease, and severe disease), and waning immunity	Number of infections, hospitalizations, and deaths
Yang et al. (2021c)	Leaky vaccine (preventing infection) and waning immunity	Numbers of infections, hospitalizations, and deaths; weekly numbers of new confirmed and probable cases
Silva et al. (2021)	Leaky vaccine (preventing infection and symptomatic disease)	ICU occupation
Więcek et al. (2021)	All-or-nothing	Numbers of infections and deaths
Du et al. (2021)	Leaky vaccine (preventing infection)	Years of life lost
Tokuda, Kuniya, and Shibuya (2021)	Leaky vaccine (preventing infection)	Numbers of new cases, deaths, and hospitalized cases

Table 3
Description of universal acronyms used in the models.

Acronym	Description
S	Susceptible individuals who are either not vaccinated or have been vaccinated but with failure or partial protection
E	Exposed individuals in the latent stage
A	Asymptomatic infectious individuals who have been infected but never develop symptom.
P	Presymptomatic infectious individuals who have been infected but have not developed symptoms yet
I	Infected individuals who have symptoms
H^m	Hospitalized individuals with mild symptoms
H^s	Hospitalized individuals with severe symptoms
Q	Quarantined individuals
D	Dead individuals from the disease
V	Vaccinated individuals who have not been infected and whose protection has not waned
R	Recovered individuals from the disease

groups with differential priority scales. By virtue of exploring real COVID-19 surveillance data, model simulation results can provide significant implications to predict which priority group should be targeted to increase health benefits. A typical approach is stratifying the population into different categories based on the characteristics of interest, for example, age or risk groups, and spatial location. Suppose there are M-groups indexed by subscripts $i = 1, 2, \cdots, M$, then a group-structured epidemiological model of each compartmental class (S_i, E_i, A_i, P_i, I_i, R_i and V_i) of a typical group i can be formulated and the diagram is illustrated in Fig. 2. In this case, the force of infection $\lambda_i(t)$ for susceptible individuals in group i can be formulated as

$$\lambda_i(t) = \beta_i \sum_{j=1}^{M} C_{ij} \frac{\beta_A A_j(t) + \beta_P P_j(t) + \beta_I I_j(t)}{N_j}.$$

Here β_i is the transmission probability of a susceptible individual in group i when contacting with an infectious individual and C_{ij} is the number of contacts individuals in group i have per unite time with individuals in group j. The proportion of individuals acquiring full protection in group i is $\rho_{iV} = \varepsilon p_i$ (vaccine efficacy parameter ε is assumed to be group-independent and there is no existing seroprevalence for simplicity) and therefore, the total number of vaccine doses administrated is $\sum_{j=1}^{M} p_j N_j$ for one-dose vaccines or $2\sum_{j=1}^{M} p_j N_j$ for two-dose vaccines, respectively.

3.1.1. Age-group based priority

Age-stratified priority vaccination is a widely investigated strategy in existing studies (Bubar et al., 2021; Choi et al., 2021b; Foy et al., 2021; Maclntyre et al., 2021). Based on a continuous-time age-stratified SEIR (susceptible, exposed, infectious, recovered) modelling framework, three different model schemes were developed under specific vaccine scenarios (Bubar et al., 2021). Two vaccines rollout modes were compared. One is a continuous rollout vaccination scheme, by distributing vaccines continuously during the on-going transmission, while the other is pre-transmission rollout vaccination, that is, allocating all available vaccines initially before the epidemic. In view of vaccine hesitancy, 30% of the population for each age group were excluded from the vaccination program. For continuous rollout vaccination, the protective efficacy of vaccines was assumed to be 90%. The whole population were assumed to be susceptible initially and 0.2% population were assumed to be vaccinated per day until the vaccines were used up. In simulations, the daily vaccination was assumed to be completed before the beginning of each day. For pre-transmission rollout scenario, two modes of imperfect vaccine efficacy were considered, which are all-or-nothing and leaky vaccine. The assumption of all-or-nothing vaccine implies that a proportion of ε vaccinated population acquired 100% percentage of protection (V^F compartment in diagram 1(a)) while $1 - \varepsilon$ percent of vaccinated individuals gain zero protection. For leaky vaccine, vaccinated individuals were assumed to be gained some percentage of protection against COVID-19 (the immunized group with partial protection in diagram 1(b)). Moreover, existing seroprevalence was incorporated by shifting the fraction of seropositive individuals into recovered compartment. Only seronegative individuals were eligible for vaccination. The seropositive individuals, vaccinated individuals with failed protection, and individuals refusing vaccination were classified into no-vaccination compartments (S_x, E_x, I_x and R_x). Individuals who have been vaccinated with effective protection were separated into vaccinated compartments (S_v, E_v, I_v and R_v). Unvaccinated compartments (S, E, I, R) contain individuals who accepted vaccination but did not receive one dose. Priority vaccination

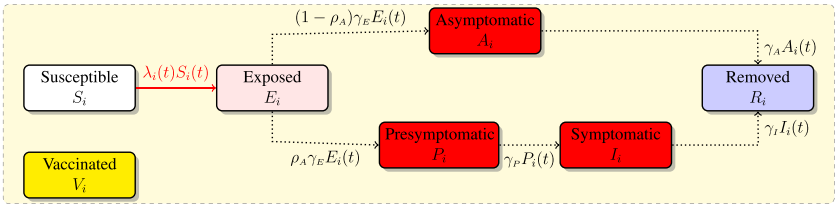

Fig. 2. The model diagram for category i in a vaccine prioritization strategy.

strategies for specific age groups and mass vaccination to all individuals were compared by changing the vaccine supply and the severity of the transmission. The simulations provided meaningful implications for optimum utilization of the limited available doses. For highly effective transmission-blocking vaccines, prioritizing vaccines to adults aged 20–49 years would bring more benefits in reducing cumulative incidence than other age groups. For most scenarios, vaccine prioritization for older adults (60+ years) would minimize mortality and years of life lost. In terms of locations with high seroprevalence, prioritized seronegative individuals would contribute to a substantial decline in mortality and disease incidences.

An age-group stratified SEAIQRDV (see Table 3 for the meaning of these compartments) transmission model was proposed in Foy et al., 2021. On account of the variability of vaccine induced immunity, two different circumstances were considered. In the case of sterilizing immunity (all-or-nothing scenario), vaccinated individuals receiving full protection would not get involved into the transmission process. For the other leaky circumstance, the vaccinated individuals would become infected due to non-sterilizing/temporal immunity. As a parameter, daily COVID-19 vaccine doses availability was coupled into the vaccinating rate to evaluate different vaccine dose distribution strategies. Mass vaccination of all population and prioritizing vaccination to three different age groups were compared under the above-mentioned two different immunity situations. Besides, combined effects of four levels of control measures were taken into consideration. Based on published COVID-19 data in India, the model was simulated by varying vaccine efficacy, the strength of control measures and vaccine deployment rate. Model simulations indicated that targeted vaccination of older adults (60+ years) would substantially decline COVID-19 caused mortality in India, which would be the optimal vaccination strategies with consideration of limited vaccine supply and Indian population structure. This result supports WHO's recommended vaccination strategy for limited vaccine supply.

In MacIntyre et al., 2021, a similar compartment (SVEIQRD) model with age specific parameters was developed to evaluate the effects of vaccination on COVID-19 spread in New South Wales, Australia. The contagious process was described by detailed classifications of infected compartment based on the evolutionary characteristics of the disease. Targeted (limited vaccine supply was given to targeted age groups), ring (vaccination of traced contacts) and mass (unlimited supply) vaccination strategies were compared by varying the model structures. The same model structure was used for targeted and mass vaccination strategy, which were differed by the different vaccination rates. For age-specific targeted vaccination, only susceptible individuals were vaccinated with constant vaccine distributing rates within the targeted age group until the vaccines were out of stock. In the case of mass vaccination, the daily distribution rates in age groups and epidemiological state were directly proportional to the number of susceptible and latent people. Compared to the above-mentioned vaccination strategies, the model structure for ring vaccination was different since only the traced individuals by contact tracing were vaccinated. Varied parameters on vaccine efficacy based on published studies (between 38% and 95%) were tested. Vaccinating the younger age group (10–29 years) would greatly reduce the cumulative cases while vaccinating older adults (65 + year-old) with higher risk of death would substantially decrease the death number. For mass vaccination, the required vaccine coverage was inversely varying with vaccine efficacy. The herd immunity could not be achieved if the vaccine efficacy was lower than 60%. In the scenario of limited vaccine supply, ring vaccination would be the optimal strategy in terms of required vaccine doses if a large proportion (at least 90%) of contacts per case was traced and vaccinated. Mass vaccination was feasible to achieve herd immunity and block community transmission if the vaccine efficacy and the rate of vaccine rollout were both high enough. The post-exposure prophylaxis (PEP) vaccine efficacy was also considered. Whether COVID-19 vaccines will be effective as PEP is unknown, but may be possible with the consideration of a long incubation period (MacIntyre et al., 2021; Wassie et al., 2020).

In Choi et al. (2021b), three more compartments (dead D, hospitalized with mild symptoms H^m and hospitalized with severe symptoms H^S) were included in addition to the SEAPIRV modelling structure, and four different age groups (age groups of 0–19, $20-49$, $50-64$ and $65+$) were considered. Five vaccination strategies were compared: no priority vaccination and allocating vaccines to each targeted age group respectively. Furthermore, the combined effects of implementing social distancing strategies were taken into account. Based on the actual COVID-19 data in Korea, model simulations indicated that the incidence would be mostly lessened if individuals with high spreading ability of COVID-19 were preferentially vaccinated. However, vaccination priority for elderly adults would bring the largest reduction in incidence when considering the joint effects of high level social distancing (SD). Irrespective of the level of SD, prioritizing vaccination to elderly age group would maximally reduce mortalities.

In Moore et al. (2021a), an age-stratified SEIRD compartmental model was proposed to simulate the transmission of SARS-CoV-2 in UK. The force of infection was determined by the age-stratified social contact matrix for UK. The infectious individuals were further classified into more classes based on symptom status. In order to match the COVID-19 outbreak data in UK, susceptibility and the probabilities of becoming symptomatic, being hospitalized and the risk of dying were assumed to be dependent on age. Age-dependent vaccine efficacy, in particular, reduced efficacy of the vaccine in older age groups, was considered. Besides, the model incorporated the effect of household isolation, which was realized by classifying primary and secondary infections within a household. In view of the increased risk of COVID-19 morbidity caused by the comorbidity conditions, the population was partitioned into two categories, those with one or more health conditions and those without. Moreover, the social-distancing measures were included by adjusting the relevant transmission parameters. The additional morbidity risk of healthcare workers (HCWs) was included by increasing the corresponding susceptibility parameters. Priority order of vaccination of age groups and prioritization of healthcare workers were considered. The simulations involved the sensitivity analysis to other key factors, including the vaccine characteristics, speed of vaccine deployment and age-dependent efficacy. In terms of minimizing future deaths and quality adjusted life years (QALYs) lost, the optimal vaccination strategy was suggested to prioritize vaccines to elder adults, which is consistent in all scenarios.

3.1.2. Risk-based prioritization

When facing the trade-offs posed by vaccine shortage, prioritization vaccination strategies of frontline workers and high-risk subgroups were proposed by policy makers, such as the Advisory Committee on Immunization Practices in the United States (Dooling et al., 2020). Evaluation the effectiveness of risk-based prioritization vaccination programs can be addressed by risk-stratified epidemiological models, which also take the group-stratified modelling structure (Fig. 2). In Wang et al. (2021), a stochastic SEIRDV model was developed to describe COVID-19 transmission dynamics under vaccination with the infectious compartment being classified into four sub-classes: asymptomatic infectious, pre-symptomatic infectious, symptomatic infectious and symptomatic infectious that are hospitalized. In order to investigate the combined effects of vaccine timing, age-risk groups prioritization on mortality rates, each (sub)compartment was separated into different subgroups based on vaccine type, ages and risk of infection. On the basis of vaccination status, individuals within each subgroup were further divided into unvaccinated, newly vaccinated with the first dose, newly vaccinated with the second dose, and fully vaccinated with the second dose. Transitions between compartments were assumed to follow Poisson distribution. COVID-19 vaccines were assumed to either protect individuals from infection (infection-blocking) or block the deterioration of the symptoms (symptom-blocking). For these two types of vaccine efficacies, three vaccination options were compared, which are no priority group, 1 of 3 priority groups vaccinated before the general public (older adults (65+ years), adults who have high-risk underlying conditions, or both) and vaccinating age-risk groups in order of risk for severe COVID-19 outcomes. The main findings suggested that the timing of vaccination rollout would substantially reduce the mortality rate compared with risk-based prioritization, and the first-dose vaccination campaign would bring more benefits in saving lives when a single dose provides high efficacy in reducing susceptibility or severity.

3.1.3. Geography-stratified prioritization

Due to regional disparity in the severity of outbreak and vaccine deliverability, the setting of the priority order for the remaining population groups differ from region to region. Therefore, geographical variations on spreading characteristics should be considered in optimizing vaccination allocations. The studied geographical region was divided into square cells distinguished by the coordinates. Within each cell i, the group-structured modelling framework illustrated in Fig. 2 remains valid and in the study Barreiro et al. (2021), the traditional SEIRSV compartmental model was employed to describe the transmission of COVID-19 under the vaccination scenario. Here, the incidence function was assumed to follow a Poisson distribution. In particular, the vaccine efficacy was assumed 100% and the vaccinated individuals within each cell were assumed to be excluded from the transmission process before moving to susceptible compartment due to waning immunity. The geographical virus spreading was caused by three mobility mechanisms between different cells, which are virus spreading to neighboring cells, long distance travels and random trips to remote areas. The mobility between different cells was assumed as a stochastic process. Different mobility parameters were employed to characterize corresponding mobility mechanisms respectively. By simulating the data of Argentina, Mexico and Spain, the main results indicated that preferentially allocating vaccine doses to the most densely populated area outperformed vaccinating homogeneously in the case of vaccine shortage. The immunity lapse of vaccinated individuals are important to vaccination timing. Moreover, the isolation of confirmed cases were shown to effectively reduce infections by extending the model with an additional isolated compartment.

In Fuady et al. (2021), an SIQRD compartmental model was used to mimic the spread of COVID-19 in Indonesia, where Q represents the size of quarantined individuals. Based on this model, four vaccine allocation scenarios were compared, which are without vaccination, fair vaccination and targeted vaccines to five and eight COVID-19 seriously attacked districts. The time period needed for accomplishing the vaccination was assumed as six and twelve months respectively. Simulation results indicated that the benefits in lowering COVID-19 incidence cases brought by targeted vaccination were the same as the case of vaccinating all people fairly. Shortening the accomplished time period for the vaccination program would be more beneficial to control the transmission of COVID-19. In the case of lacking available vaccines, targeted vaccine allocation to regions with high COVID-19 incidences could bring more benefits by the COVID-19 vaccination program.

3.2. Time-varying prioritization

Due to the prevalence of new variants of SARS-CoV-2 virus, many countries have encountered recurrent outbreaks of COVID-19 (Bontempi, 2021; Ghanbari, 2020; Huang & Qi, 2020; Vaid et al., 2020; Yu, Qi, & Hu, 2020). As a consequence, the vaccination strategy should be flexible and respond quickly to the resurgence of COVID-19 (Mandal et al., 2021). Subject to limited vaccination capacity, priority groups for vaccination should possibly switch along with the evolution of epidemics, i.e., dynamically adapting the vaccine allocation to different targeted groups (Han et al., 2021).

An agent-based computational SVEPAIHQRD model was developed in Lee et al. (2021) to simulate the COVID-19 propagation under the impact of a series of interventions such as vaccination, treatment, quarantine and other NPIs. In particular, the vaccination was assumed to be implemented inside the point-of-dispensing sites (POD). The contact rates were assumed to be different intra-POD and outer-POD, where the transmission process was modeled respectively. A mixed vaccination strategy was investigated in the study, that is, preferentially distributed vaccines to the high-risk population, and then switched to the equal distribution among the remaining public. The prioritized high-risk population contain health-care workers, 65+ years old elders, patients younger than 65 but with high health conditions. It was assumed to dynamically switch between the prioritized and non-prioritized strategies and initially, the proportion of vaccine were allocated to the

high-risk population. Numerical optimization method was employed to seek the optimal switch threshold that the overall attack and mortality rates were minimized in the case of a constrained vaccine storage. Vaccine induced protective immunity was assumed to be varying from person to person. The findings indicated that delayed and inefficient vaccine delivery could substantially impede the intervention effort. Employing an optimal mixed strategy could significantly reduce the attack and mortality rates. The sensitivity analysis illustrated that the optimal mixed strategy was quite robust against variations in model parameters.

In Han et al. (2021), a data-driven deterministic compartmental model paired with optimization theory was developed to explore the optimal priority vaccination strategy in China. A 17 age-group SIRV model, with an additional compartment to denote the individuals who have received at least one dose of the two-dose vaccine but have yet to develop protection, was proposed. Compared to traditional strategies of random mass vaccination, a dynamically adaptive vaccination allocation in different age groups could provide a larger reduction of COVID-19 burden when the vaccine supply was limited.

In Mandal et al. (2021), the predicted impact of rapid-response vaccination strategy was investigated based on a 3 age-group SEAPIRV deterministic model and real COVID-19 data in India. It was assumed that vaccination campaign would be triggered when the test positivity rate reached a critical threshold from sentinel sites (for example test centers at district hospitals). Here the test positivity rate denotes the proportion of symptomatic individuals with COVID-19 among all individual with COVID-19-related symptoms. Three immunity status were considered, unvaccinated, vaccinated but not yet immuned, and vaccinated with immunity protection, and three scenarios related to control efforts were explored, no intervention, responsive vaccination and responsive vaccination plus NPIs. Simulation results demonstrated flexible vaccine distribution could maximize the impact of limited vaccination resources in the context of a rapidly evolving epidemic.

3.3. Dose stretching: delaying the second dose

To surmount long-lasting inadequate supply of COVID-19 vaccines, besides the priority vaccination strategy, some countries attempted to maximally stretch the protective effects of available vaccines by prioritizing first doses and delaying the second dose (Saad-Roy et al., 2021; The Lancet Infectious Dis, 2021) for two-dose COVID-19 vaccines. Two key relevant issues are: (i) whether vaccinating more individuals with the first dose of available vaccines and delaying the second dose will generate improved impact on containing COVID-19; (ii) what is the optimal delayed period of the second dose. These two issues can be addressed with mathematical models. The modelling ideas in most related studies is to distinguish the vaccine efficacy for individuals receiving first dose and receiving two dose series, or to consider the waning immunity after the first shot.

A 6-age-group agent-based model was proposed in Moghadas et al. (2021) to compare the impact of two vaccination strategies: delaying the second dose (DSD) and continuing the recommended 2-dose series. Using published results on the waning efficacy of Moderna and Pfizer-BioNTech vaccines following the first dose against all infection, symptomatic disease, and severe disease, simulations were performed with differential levels of preexisting immunity in the population with varying delay in second dose from recommended schedule. Under the assumption of long-lasting efficacy of first dose, DSD of Moderna and Pfizer-BioNTech vaccines both substantially reduced infections, hospitalizations and deaths provided that the efficacy of the vaccine was not low. To maximally mitigate the severity of COVID-19, the optimal time period of DSD was recommended as 12–15 weeks. In the case of waning efficacy of first dose, DSD of Moderna vaccine outperformed Pfizer-BioNTech vaccine in averting the severe outcomes of COVID-19.

A meta-population SEIRSV network model with age-structure was proposed in Yang et al. (2021c) to simulate how priority (65+ years) vaccination policies influence the COVID-19 pandemic amidst the prevalence of new SARS-CoV-2 variants in New York City. A wide variety of factors were considered in simulations, including seasonality, pre-testing antibodies of individuals with recent infection, waning immunity of prior infection and delaying the second dose. The simulations highlighted several significant implications for COVID-19 vaccination. On one hand, in order to greatly reduce the hospitalizations and deaths, the available COVID-19 vaccines should be given firstly to 65+ years population ahead of other age-groups. On the other hand, delaying the second dose would substantially mitigate the severity of the pandemic in case of future COVID-19 vaccine shortage in the New York City.

An optimization model (based on an age-group SEIR dynamic model) was proposed in Silva et al. (2021) to determine the optimal delay duration between the first and second COVID-19 vaccine doses. Intensive care unit (ICU) admission serves as the key evaluation index to compare the selected optimal delay duration with the standard delay of 4 weeks. Lenient social distancing and some targeted vaccinated age groups were assumed in the study. Simulation results indicated that both the vaccine mechanism of action and first-dose efficacy affected the determination of delay. Two types of protective effects of vaccines were explored, blocking infection and alleviating symptoms of COVID-19 respectively. The optimal delay for the second dose was recommended as no less than 8 weeks for both types of vaccines, the difference of which lied in the scale of first dose efficacy on blocking infection and blocking symptom respectively.

3.4. Dose sparing: fractional dosing strategy

Latest experimental findings indicated that the neutralization antibodies of B.1.617.2 (Delta) variant induced by a single dose is limited (Liu et al., 2021a). Moreover, recent researches on COVID-19 vaccine effectiveness against B.1.617.2 (Delta) variant showed that fully immunized population with completed two-doses acquire significantly higher protection than

those of partially immunized with only one dose (Jara et al., 2021; Lopez Bernal et al., 2021). These evidences indicate that partial immunity induced by first dose alone may be insufficient to restrain the prevalence of new variants of SARS-CoV-2. Compared to delaying the second dose strategy, dividing one single dose vaccine into more fractional doses with certain efficacy can enlarge the vaccination coverage, which facilitates the acquisition of full immunity (Więcek et al., 2021). A five-fold fractional-dose yellow fever vaccination campaign was launched at 2404 vaccination sites in Kinshasa from August 17 through August 26, 2016, and it was shown that fractional-dose vaccination is a viable approach for containing yellow fever outbreaks (Casey et al., 2019). Based on previous practical experiences from using reduced 1/5 dosage in combating yellow fever (WHO, 2016), WHO recently came up with similar dosing-sparing strategies in response to the worldwide limited COVID-19 vaccine supply (WHO, 2021a). Currently, there are few existing experimental evidences in finding proper fractional COVID-19 vaccine dosage that could have indistinctive immune response compared to the case of one standard dose (Jackson et al., 2020; Khoury et al., 2021; Voysey et al., 2021). There have been some modelling studies on the effectiveness of fractional dosing on disease control (Chen, Liu, Liu, & Lou, 2020). In Więcek et al. (2021), an age-grouped SEIDRV model was proposed to explore the impact of three dose stretching approaches, which are fractional dosing vaccination, delaying the second dose and using available vaccines rather than waiting for higher efficacy ones. The vaccinated group was further divided into two classes, those protected by vaccine and vaccinated but not protected. Simulation results indicated that doubling or quadrupling the vaccination rate through fractionating doses would dramatically reduce infections and mortality. Regardless of the vaccine efficacy, this dose-sparing vaccination strategy by deploying fractional dose vaccine is especially beneficial for less-developed countries, many of which are at the back of the vaccine queue. Another age-grouped SEAPIHRDV modelling study (Du et al., 2021) estimated the cost-effectiveness of SARS-CoV-2 vaccine dose fractionation in India. The vaccine cost and willingness to pay per Years of Life Lost (YLL) averted were fed into model simulation to determine the optimal dose fraction under various vaccine efficacies and transmission scenarios. It was shown that the dose fraction was cost-effective for mitigating the pandemic and saving a large number of lives.

Based on an age-grouped SEIR transmission model with a varying vaccinating rate, the possible effects of alternative strategies for COVID-19 vaccination were compared, which are either extending the time interval between the first and second dose or using low (half a standard) dose vaccines (Tokuda et al., 2021). Compared to the interval extension strategy, half a dose strategy could delay the peak of the hospitalization and mortality cases to a greater extent.

4. Discussion

Mathematical modelling has shown to be a powerful tool in exploring the spreading mechanism of COVID-19 and possible impacts of various intervention strategies. Along with advancing virological research of SARS-CoV-2 and accumulating data, transmission models have been enriched from classic SIR compartmental models to age-structured SEAPIHQRV models, and more detailed agent-based models. Recent advances on SARS-CoV-2 research further make it possible to formulate and calibrate jurisdiction-specific models. Under a shortage scenario, proper vaccination strategies can be designed with the aid of modelling studies, which can substantially reduce the health and economic impacts of the pandemic. The current manuscript mainly focuses on reviewing different modelling methodologies to describe potential vaccination strategies for optimizing the immunization effectiveness. It should be noted that model-based projections should be carefully interpreted in terms of modelling assumptions. For example, some studies assumed high asymptomatic rates for specific coronavirus strains, due to following aspects including but not limited to: (i) some early studies overestimated the asymptomatic rate due to limited understanding on asymptomatic infection; (ii) data for asymptomatic rate were retrieved from some particular population with higher percentage of asymptomatic infections in nursing home residents or staff, air or cruise travelers, or groups younger than 39 years (Ma et al., 2021).

Various approaches are possible to maximize effectiveness of immunization strategies, including prioritization strategies on specific groups characterized by age, risk, geography, switching prioritization, dose stretching, and dose sparing. Furthermore, the policy should be made based on the outcome measures and the efficacy of available vaccines. In general, a time-varying priority vaccination strategy would be a better one when the vaccination capacity is constrained. Delaying the second dose may be a good choice if the vaccine-induced immunity does not decay rapidly. Covering a larger proportion of individuals by fractional dosing would be proper if the high-level of vaccine efficacy can be guaranteed. Due to limited vaccination capacity and leakiness of vaccines, NPIs should be maintained in addition to a vaccination program.

In view of waning immunity and incessant new variants of SARS-CoV-2, booster vaccination by giving one extra shot to fully vaccinated individuals has been put on the agenda (Krause et al., 2021). Some small scale clinical trials revealed that extra dose of BNT162b2 vaccine could efficiently boost immunity in both healthy adults and patients with cancer or solid tumors (Arbel et al., 2021; Choi et al., 2021a; Shapiro et al., 2021; Shroff et al., 2021). Although existing evidences on the safety and effectiveness of booster vaccination are limited, more than 120 high- or upper middle-income countries have implemented the booster shots campaign (WHO, 2021a). However, ethical issues raised by booster vaccination should be noticeable, that is, global vaccine inequity will be exacerbated due to heavy demand of booster doses. On account of global constrained vaccine supplies, WHO appealed for postponing large-scale booster programs (WHO, 2021a). Therefore, it is imperative to seek for alternative booster strategies such as heterologous vaccination (Liu et al., 2021b) and usage of oral/intranasal vaccines (Langel et al., 2021). In reality, other factors should be considered in designing an appropriate immunization program during the vaccine shortage period. It was shown in many studies that vaccine prioritization should be given to the older adults to minimize mortality and years of life lost (Bubar et al., 2021). Despite the mortality risks, older nurses are

less likely than younger nurses to take the vaccine against COVID-19 (Chan, Wong, & Wong, 2021). Vaccine hesitancy should be included when a vaccination strategy is designed.

Moreover, many countries have implemented regular testing/screening policies for unvaccinated individuals, which pose important topics on using supplementary screening policy to compensate negative impacts of vaccination shortage. An interesting issue that remains to be addressed is whether regular testing/screening plays certain or even equivalent preventing roles as vaccination. If that is the case, regular testing/screening can serve as an aiding control measure to temporarily relieve current crisis of COVID-19 vaccine shortage in post-vaccination era. However, concurrent vaccination and regular testing will bring a big challenge in modelling, in particular when the testing frequency and sensitivity are involved. Another interesting problem is to optimize the vaccination scheme for multiple-dose vaccines on the individual level (Faro-Viana et al., 2022; Leng et al., 2021), that is, to determine of optimal individual vaccination scheme through modelling. All these situations pose interesting questions for further studies on the topic.

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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