EVALUATING VACCINATION EFFECTIVENESS OF GROUP-SPECIFIC FRACTIONAL-DOSE STRATEGIES

ZHIMIN CHEN*
School of Mathematics and Systems Science
Guangdong Polytechnic Normal University
Guangzhou, 510665, China
School of Mathematical Sciences, South China Normal University
Guangzhou, 510631, China

KAIHUI LIU
Faculty of Science, Jiangsu University
Zhenjiang, Jiangsu, 212013, China

XIUXIANG LIU
School of Mathematical Sciences, South China Normal University
Guangzhou, 510631, China

(Communicated by Shigui Ruan)

Abstract. In this paper, we formulate a multi-group SIR epidemic model with the consideration of proportionate mixing patterns between groups and group-specific fractional-dose vaccination to evaluate the effects of fractionated dosing strategies on disease control and prevention in a heterogeneously mixing population. The basic reproduction number \( R_0 \), the final size of the epidemic, and the infection attack rate are used as three measures of population-level implications of fractionated dosing programs. Theoretically, we identify the basic reproduction number, \( R_0 \), establish the existence and uniqueness of the final size and the final size relation with \( R_0 \), and obtain explicit calculation expressions of the infection attack rate for each group and the whole population. Furthermore, the simulation results suggest that dose fractionation policies take positive effects in lowering the \( R_0 \), decreasing the final size and reducing the infection attack rate only when the fractional-dose influenza vaccine efficacy is high enough rather than just similar to standard-dose. We find evidences that fractional-dose vaccination in response to influenza vaccine shortages take negative community-level effects. Our results indicate that the role of fractional dose vaccines should not be overestimated even though fractional dosing strategies could extend the vaccine coverage.

2020 Mathematics Subject Classification. Primary: 37N25, 34C60; Secondary: 92D40.

Key words and phrases. multi-group epidemic model, fractional-dose vaccines, group-specific vaccination, the final size.

Supported in part by the International Training Project for Outstanding Young Scientific Research Talents in Guangdong Universities in 2018 at South China Normal University, the NNSF of China, the Research Grants of Jiangsu University, the NSF of Guangdong Province and the General Program of the Natural Science Foundation of Guangdong Province of China.

* Corresponding author: Zhimin Chen.
1. Introduction. Vaccination, as one of the most efficient control strategies, has greatly reduced the prevalence of infectious diseases worldwide. The lack of sufficient vaccines at the outset of a new pandemic prompts the use of dose fractionation to stretch vaccine supplies and enhance herd immunity. The recent substantial outbreaks of yellow fever in Angola led to a global shortage of vaccine stockpiles, which pushes the World Health Organization (WHO) to adopt five-fold dose fractionation for its vaccination campaign in Kinshasa, Democratic Republic of the Congo, in July–August, 2016 [34]. In early 2016, the WHO announced a global shortage of inactivated poliovirus vaccine, and India was the first country in the world to introduce fractional-dose inactivated poliovirus vaccine into its immunization programme [9]. Lower-dose vaccines have drawn great attention and a series of explorations have already been carried out on the reduced-dose vaccines in the last few decades. By virtue of long-term trials, researchers have investigated the safety and immunogenicity of reduced/lower dose vaccines for a variety of infectious diseases, which includes partial dose influenza vaccines [12, 16, 35], lower dose yellow fever vaccines [2, 22, 30, 31], one-fifth fractional dose poliovirus vaccines [23, 28] and small-dose meningococcal vaccines [8, 13]. These research findings indicate that reduced-dose vaccines are safe and can provide similar immunogenicity as standard-dose. Under the circumstances of limited vaccine stockpiles, dose fractionation vaccination policy could be considered as a feasible vaccination strategy in response to emergency epidemics by effectively extending the overall coverage of vaccines.

In the real world, the evolution of an epidemic is influenced by many different levels of heterogeneity in populations [4, 21]. Individuals in the populations differ various aspects such as age, gender, genetic, behavior, and immunological feature, which lead to persistent differences among individuals in their activity levels [4], susceptibility (immunity) and infectivity [11], and even recovery ability [7]. These heterogeneities within populations may have significant influences on the transmission of infectious diseases [4]. Moreover, the increasing connectivity between different groups makes the control and prevention of infectious diseases increasingly difficult [4]. Consequently, heterogeneities within and between populations should be taken into consideration in epidemic models.

Mathematical models describing the dynamics of infectious diseases have played an important role in better understanding epidemiological patterns and disease control for a long time. Various heterogeneous epidemic models have been proposed and explored extensively to study the transmission dynamics. In Chow et al. [4], a multi-group Susceptible-Infectious-Recovered (SIR) epidemiological model was proposed to appraise the effects of group-targeted vaccination strategies on disease control and prevention. The authors also illustrated reproduction numbers with different meanings can be utilized to examine the influence of population heterogeneities such as group preferences, activity levels, and mixing patterns. The authors in [6] investigated the global stability of a class of multi-group vaccination epidemic models with delays by constructing the global Lyapunov functionals via a graph theoretical approach. Lee et al. [17] adopted the optimal control theory to explore the most efficient ways to utilize the influenza vaccine under the impact of limited vaccine supply. An SIR epidemic model with a nonlinear pulse vaccination was proposed and analyzed to examine how limited vaccine resources affect the transmission and control of emerging infectious diseases [25]. In Yu et al. [36], the authors explored the global dynamics of a multi-group SIR epidemic model by using the Lyapunov-LaSalle principle and studied the optimal control strategy of
an infectious disease with the mixing of two sub-groups under limited vaccination resources. Even though considerable progress has been achieved in the studies of the impact of vaccination strategies on disease control, few work focused on evaluating the impact of fractionated dosing vaccination policies on disease transmission and control in a heterogeneously mixing population with limited vaccination resources. Recently, Chen et al. [3] developed a single-group SIR model incorporating fractional-dose vaccine efficacy. In this paper, we extend the ideas in [3] to formulate a multi-group SIR model with the consideration of population heterogeneities and group-specific fractionated vaccination strategies. For this purpose, we systematically analyze both individual-level effects (i.e., vaccine efficacy) of different fractionated doses and population-level implications of fractional-dose vaccination programs. Based on the proposed mathematical model, we derive the formulation for the basic reproductive number $R_0$, establish the existence and uniqueness of the epidemic final size and its relationship between $R_0$, and find explicit expressions to calculate the infection attack rates for each group and the total population. We further perform numerical simulations based on the model to examine the effects of group-specific fractionated dosing vaccination on control of the 1957–1958 pandemic Asian influenza A (H2N2).

The rest of this paper is structured as follows. In the next section, we present a derivation of our model with heterogeneous mixing and group-specific fractional-dose vaccination. In section 3, we show theoretical analysis involving the existence and uniqueness of the final size, the expression for $R_0$, the relationship between them, and the calculation formulation of the infection attack rates. Section 4 is devoted to numerical simulations and sensitivity analysis. The paper ends with a summary of our results and a short discussion on possible extensions of our model and results.

2. Formulation of a multi-group SIR model. Suppose that the total number of individuals in the population is $N (> 0)$. The population is classified into three classes, that is, susceptible ($S$), infected ($I$) and recovered ($R$) classes. The vaccination strategy we choose is a single pre-pandemic vaccination campaign for susceptible population only. This vaccination programme is required to be completed before the outbreak of the infectious disease. To consider population heterogeneities, the susceptible class is segmented into distinct $K$ groups according to some criteria (e.g. ages) in the implementation of the group-specific fractionated vaccination strategy, where $K$ is a given positive integer. We assume that each standard-dose vaccine can be effectively fractionated into $n_l$ ($\in \mathbb{Z}^+$) fold for $l$-th group, $1 \leq l \leq K$. Let $p_l$ be the proportion of population that standard dose vaccines can cover in $l$-th group. Then, $n_l p_l$ ($\leq 1$) represents the coverage of fractional-dose vaccines in $l$-th group.

Let $S_{0l} (> 0)$ denote the number of susceptible individuals initially (i.e., before the vaccination campaign) in $l$-th group. After the vaccination campaign, the susceptible population in $l$-th group can be classified into three classes, which are the $V^{(l)}$-class of vaccinated individuals with full protection, the $S^{(l)}$-class of vaccinated individuals with partial protection and the $S_{u}^{(l)}$-class vaccinated individuals experiencing vaccine failure or unvaccinated individuals. Here, we assume either the standard dose or the fractional dose vaccine does not wane during the epidemic, which implies that vaccinated individuals with full protection will not be
involved in the transmission of the infectious disease. Thus, the number of individuals in $V^{(l)}$-class remains unchanged during the course of the epidemic, that is, $V^{(l)}(t) \equiv V^{(l)}(0)$ for all $t \geq 0$, where $V^{(l)}(0) = V^{(l)}(0)$. More concretely, the compartment in our model and their initial values are given in Table 1. Additionally, the mixing pattern between subpopulations is assumed as proportionate mixing. During the course of epidemics, individuals in the $S_u^{(l)}$ and $S_v^{(l)}$ subgroups can be infected by contacting with infectious individuals in either the $I_u^{(m)}$-class or $I_v^{(m)}$-class, where $1 \leq l, m \leq K$. The transfer diagram of the system is shown in Fig. 1.

To quantify different aspects of group-specific fractional dose vaccines in individual level, we introduce $5K$ pairs of notations, that is, $(p_c^{(l)}, \varepsilon_c^{(l)}(n_l)), (p_f^{(l)}, \varepsilon_f^{(l)}(n_l))$, $(p_i^{(l)}, \varepsilon_i^{(l)}(n_l))$, $(p_u^{(l)}, \varepsilon_u^{(l)}(n_l))$, and $(p_v^{(l)}, \varepsilon_v^{(l)}(n_l))$, where $l \in \{1, \ldots, K\}$ and $n_l \in \mathbb{Z}^+$. Here, $p_c^{(l)}$ denotes the probability that a standard dose vaccine takes effects on the individuals in $l$-th group. Then, $\varepsilon_c^{(l)}(n_l)$ is introduced to describe the relative reduction in the probability of a $n_l$-fold fractional dose vaccine taking effects to that of a standard dose vaccine. $p_f^{(l)}$ is the probability that a vaccinated individual receiving a standard dose vaccine gains full protection given that this vaccine takes effects. The meaning of $\varepsilon_f^{(l)}(n_l)$ is analogous to that of $\varepsilon_c^{(l)}(n_l)$, which measures the relative reduction in the probability that a $n_l$-fold fractional dose vaccine provides

| Compartment | Definition | Initial Value |
|-------------|------------|---------------|
| $S_u^{(l)}(t)$ | Total number of susceptible individuals in the $l$-th group who are unvaccinated or experiencing vaccine failure (i.e., the vaccine takes no effect in protecting the vaccinated individual from infection) at time $t$ | $S_u^{(l)}(0)$ |
| $I_u^{(l)}(t)$ | Total number of individuals in the $l$-th group and in the infectious stage who are not vaccinated or experiencing vaccine failure at time $t$ | $I_u^{(l)}(0)$ |
| $S_v^{(l)}(t)$ | Total number of susceptible individuals in the $l$-th group who are vaccinated and then gain partial protection at time $t$ | $S_v^{(l)}(0)$ |
| $I_v^{(l)}(t)$ | Total number of individuals in the $l$-th group and in the infectious stage who are vaccinated and then gain partial protection at time $t$ | $I_v^{(l)}(0)$ |
| $V^{(l)}(t)$ | Total number of individuals in the $l$-th group who are vaccinated and then gain full protection at time $t$ | $V^{(l)}(0)$ |
| $R(t)$ | Total number of recovered individuals at time $t$ | 0 |
Figure 1. The transition diagram of the group-specific fractional-dose vaccination model with $K$ mixed groups. In $l$-th group, the flux of new infected individuals in subgroups $I_u^{(l)}$ and $I_v^{(l)}$ are denoted as $F_{UI}^{(l)} = \sum_{m=1}^{K} \frac{c_{ul} \epsilon_{im}}{N} \left(I_u^{(m)} + p_i^{(m)} \epsilon_{i} (n_m) I_v^{(m)} \right) S_u^{(l)}$ and $F_{VI}^{(l)} = \sum_{m=1}^{K} \frac{c_{vl} \epsilon_{im}}{N} \left(I_u^{(m)} + p_i^{(m)} \epsilon_{i} (n_m) I_v^{(m)} \right) S_v^{(l)}$ respectively. While the flux of new recovered individuals in compartment $R$ from subgroup $I_u^{(l)}$ and subgroup $I_v^{(l)}$ are respectively represented as $F_{UR}^{(l)} = \gamma_l I_u^{(l)}$ and $F_{VR}^{(l)} = \gamma_l p_r^{(l)} \epsilon_{i} (n_l) I_v^{(l)}$, where $l = 1, \ldots, K$. 

\[ F_{UI}^{(l)} = \sum_{m=1}^{K} \frac{c_{ul} \epsilon_{im}}{N} \left(I_u^{(m)} + p_i^{(m)} \epsilon_{i} (n_m) I_v^{(m)} \right) S_u^{(l)} \]

\[ F_{VI}^{(l)} = \sum_{m=1}^{K} \frac{c_{vl} \epsilon_{im}}{N} \left(I_u^{(m)} + p_i^{(m)} \epsilon_{i} (n_m) I_v^{(m)} \right) S_v^{(l)} \]

\[ F_{UR}^{(l)} = \gamma_l I_u^{(l)} \]

\[ F_{VR}^{(l)} = \gamma_l p_r^{(l)} \epsilon_{i} (n_l) I_v^{(l)} \]
Correspondingly, individual receiving a standard dose vaccine to that of an unvaccinated individual.

With nonnegative initial conditions for each model (1) as below.

\[
\begin{align*}
    \frac{dS_{u}(t)}{dt} &= - S_{u}(t) \sum_{m=1}^{K} \frac{c_{l}\beta_{lm}}{N} \left( I_{u}^{(m)}(t) + p_{l}^{(m)}\varepsilon_{i}^{(m)}(n_{m}) I_{v}^{(m)}(t) \right), \\
    \frac{dI_{u}(t)}{dt} &= S_{u}(t) \sum_{m=1}^{K} \frac{c_{l}\beta_{lm}}{N} \left( I_{u}^{(m)}(t) + p_{l}^{(m)}\varepsilon_{i}^{(m)}(n_{m}) I_{v}^{(m)}(t) \right) - \gamma_{l} I_{u}(t), \\
    \frac{dS_{v}(t)}{dt} &= - p_{v}^{(l)}\varepsilon_{s}^{(l)}(n_{l}) S_{v}(t) \sum_{m=1}^{K} \frac{c_{l}\beta_{lm}}{N} \left( I_{u}^{(m)}(t) + p_{l}^{(m)}\varepsilon_{i}^{(m)}(n_{m}) I_{v}^{(m)}(t) \right), \\
    \frac{dI_{v}(t)}{dt} &= p_{v}^{(l)}\varepsilon_{s}^{(l)}(n_{l}) S_{v}(t) \sum_{m=1}^{K} \frac{c_{l}\beta_{lm}}{N} \left( I_{u}^{(m)}(t) + p_{l}^{(m)}\varepsilon_{i}^{(m)}(n_{m}) I_{v}^{(m)}(t) \right) - \gamma_{l} p_{v}^{(l)}\varepsilon_{r}^{(l)}(n_{l}) I_{v}(t), \quad l = 1, \ldots, K, \\
    \frac{dR(t)}{dt} &= \sum_{l=1}^{K} \gamma_{l} \left( I_{u}^{(l)}(t) + p_{v}^{(l)}\varepsilon_{r}^{(l)}(n_{l}) I_{v}^{(l)}(t) \right),
\end{align*}
\]

(1)

with nonnegative initial conditions for each \( l = 1, \ldots, K, \)

\[
\begin{align*}
    S_{u}(0) &= \left( 1 - p_{e}^{(l)}\varepsilon_{e}^{(l)}(n_{l})p_{v}^{l} \right) S_{u}^{(l)} > 0, \quad I_{u}^{(l)}(0) = I_{u0}^{(l)} \geq 0, \\
    S_{v}(0) &= p_{v}^{(l)}\varepsilon_{e}^{(l)}(n_{l}) \left( 1 - p_{f}^{(l)}\varepsilon_{f}^{(l)}(n_{l}) \right) n_{l}p_{l}S_{u}^{(l)} = S_{v0}^{(l)} \geq 0, \quad I_{v}^{(l)}(0) = I_{v0}^{(l)} \geq 0, \\
    R(0) &= 0.
\end{align*}
\]

(2)

Remark 1. In view of the above statements of parameters and initial values, we have \( V^{(l)}(t) = V_{0}^{(l)} = S_{0}^{(l)} - S_{u0}^{(l)} - S_{v0}^{(l)} = p_{e}^{(l)}\varepsilon_{e}^{(l)}(n_{l}) p_{f}^{(l)}\varepsilon_{f}^{(l)}(n_{l}) n_{l}p_{l}S_{u0}^{(l)} > 0, \)

\[
I_{0}^{(l)} = I_{u0}^{(l)} + I_{v0}^{(l)} = N_{0}^{(l)} - S_{0}^{(l)} \geq 0, \quad \text{and} \quad pN = p \sum_{i=1}^{K} N_{i}^{(l)} = \sum_{i=1}^{K} p_{l}N_{0}^{(l)} > 0, \quad \text{where} \quad l = 1, \ldots, K.
\]

3. Theoretical results. This section is devoted to presenting main mathematical theory results, which involves the following aspects: (1) the well-posedness of the model system, (2) the existence and uniqueness of the final size, (3) the basic reproduction number and its relation with the final size, (4) the calculation form for the infection attack rate (IAR) of the epidemic.

Denote

\[
S(t) = \left[ S_{u}^{(1)}(t), \ S_{v}^{(1)}(t), \ldots, \ S_{u}^{(K)}(t), \ S_{v}^{(K)}(t) \right]^T,
\]
Table 2. Description of the parameters in the model \((1 \leq l, m \leq K)\)

| Parameter | Definition | Range |
|-----------|------------|-------|
| \(N\)    | Number of individuals in the total population | \((0, \infty)\) |
| \(p\)    | Proportion of population that standard-dose vaccines can cover for the total population | \((0, 1]\) |
| \(p_l\)  | Vaccine coverage achievable with standard-dose vaccines for \(l\)-th group subpopulation | \((0, 1]\) |
| \(n_l\)  | Fractionation number by each standard-dose vaccine for \(l\)-th group subpopulation \((n_l p_l \leq 1)\) | \([1, 5]\) |
| \(c_l\)  | Number of contacts per unit time an individual in the \(l\)-th group makes | \((0, \infty)\) |
| \(\beta_{lm}\) | Probability of infection given contact between a susceptible individual in the \(l\)-th group and an infected individual in the \(m\)-th group | \((0, 1]\) |
| \(\gamma_l\) | Recovery rate of infective individuals without vaccine protection in the \(l\)-th group | \((0, \infty)\) |
| \(p^{(l)}_e\) | Probability that a standard-dose vaccine takes effects for individuals in the \(l\)-th group | \((0, 1]\) |
| \(\varepsilon^{(1)}_l(n_l)\) | The ratio of the probability that a standard-dose vaccine taking effects in the \(l\)-th group relative to that a standard-dose vaccine taking effects in the same group | \((0, 1]\) |
| \(p^{(l)}_f\) | Probability that a successfully vaccinated individual with a standard-dose vaccine gains full protection in the \(l\)-th group | \((0, 1]\) |
| \(\varepsilon^{(1)}_l(n_l)\) | The ratio of the probability that a successfully vaccinated individual in the \(l\)-th group gains full protection with a \(n_l\)-fold fractional-dose vaccine relative to that with a standard-dose vaccine in the same group | \((0, 1]\) |
| \(p^{(l)}_t\) | The ratio of the transmissibility of a vaccinated individual with a standard-dose vaccine in the \(l\)-th group relative to that of an unvaccinated individual in the same group | \((0, 1]\) |
| \(\varepsilon^{(1)}_l(n_l)\) | The ratio of the transmissibility of a vaccinated individual with a \(n_l\)-fold fractional-dose vaccine in the \(l\)-th group relative to that of an unvaccinated individual in the same group | \([1, 1/p^{(l)}_t]\) |
| \(p^{(l)}_s\) | The ratio of susceptibility of a vaccinated individual in the \(l\)-th group with a standard dose vaccine relative to that of an unvaccinated individual in the same group | \((0, 1]\) |
| \(\varepsilon^{(1)}_l(n_l)\) | The ratio of susceptibility of a vaccinated individual with an \(n_l\)-fold fractional-dose vaccine in the \(l\)-th group relative to that with a standard-dose vaccine in the same group | \([1, 1/p^{(l)}_s]\) |
| \(p^{(l)}_r\) | The ratio of the recoverability of a vaccinated individual in the \(l\)-th group relative to that of an unvaccinated individual in the same group | \([1, \infty)\) |
| \(\varepsilon^{(1)}_l(n_l)\) | The ratio of the recoverability of a vaccinated individual with an \(n_l\)-fold fractional-dose vaccine in the \(l\)-th group relative to that with a standard-dose vaccine in the same group | \([1/p^{(l)}_r, 1]\) |

\[
I(t) = \begin{bmatrix}
I^{(1)}_u(t), & I^{(1)}_v(t), & \ldots, & I^{(K)}_u(t), & I^{(K)}_v(t)
\end{bmatrix}^T
\]

Thus, it follows that their initial values are

\[
S(0) = \begin{bmatrix}
S^{(1)}_u(0), & S^{(1)}_v(0), & \ldots, & S^{(K)}_u(0), & S^{(K)}_v(0)
\end{bmatrix}
\]
with initial conditions $S_\tau^{(1)}, S_\tau^{(1)}(0), \ldots, S_\tau^{(K)}(0), S_\tau^{(K)}(0) \Big) \in \mathbb{R}^{2K},$

$I(0) = \begin{bmatrix} I_u^{(1)}(0), I_v^{(1)}(0), \ldots, I_u^{(K)}(0), I_v^{(K)}(0) \end{bmatrix}^T$

$= \begin{bmatrix} I_u^{(1)}, I_v^{(1)}, \ldots, I_u^{(K)}, I_v^{(K)} \end{bmatrix}^T \in \mathbb{R}^{2K}.$

Additionally, the disease recovery mechanism is described by the column vector $\Gamma = \begin{bmatrix} \gamma_1, \gamma_1 p_r^{(1)} (n_1), \ldots, \gamma_K p_r^{(K)} (n_K) \end{bmatrix}^T,$

and the epidemic transmission structure is expressed by the following matrix

$$\Phi = \begin{bmatrix}
\frac{c_1 \beta_{11}}{N} & \frac{c_1 \beta_{11} \xi_1}{N} & \frac{c_1 \beta_{12}}{N} & \frac{c_1 \beta_{12} \xi_2}{N} & \ldots & \frac{c_1 \beta_{1K}}{N} & \frac{c_1 \beta_{1K} \xi_K}{N} \\
\frac{c_1 \beta_{11} \xi_1}{N} & \frac{c_1 \beta_{11} \xi_1 \xi_1}{N} & \frac{c_1 \beta_{12} \xi_2}{N} & \frac{c_1 \beta_{12} \xi_2 \xi_2}{N} & \ldots & \frac{c_1 \beta_{1K} \xi_K}{N} & \frac{c_1 \beta_{1K} \xi_K \xi_K}{N} \\
\frac{c_1 \beta_{21}}{N} & \frac{c_2 \beta_{21} \xi_2}{N} & \frac{c_1 \beta_{22}}{N} & \frac{c_2 \beta_{22} \xi_2}{N} & \ldots & \frac{c_2 \beta_{2K} \xi_K}{N} & \frac{c_2 \beta_{2K} \xi_K \xi_K}{N} \\
\frac{c_2 \beta_{21} \xi_1}{N} & \frac{c_2 \beta_{21} \xi_1 \xi_1}{N} & \frac{c_2 \beta_{22} \xi_2}{N} & \frac{c_2 \beta_{22} \xi_2 \xi_2}{N} & \ldots & \frac{c_2 \beta_{2K} \xi_K}{N} & \frac{c_2 \beta_{2K} \xi_K \xi_K}{N} \\
\vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
\frac{c_K \beta_{K1}}{N} & \frac{c_k \beta_{K1} \xi_1}{N} & \frac{c_k \beta_{K2}}{N} & \frac{c_k \beta_{K2} \xi_2}{N} & \ldots & \frac{c_k \beta_{KK}}{N} & \frac{c_k \beta_{KK} \xi_K}{N} \\
\frac{c_k \beta_{K1} \xi_1}{N} & \frac{c_k \beta_{K1} \xi_1 \xi_1}{N} & \frac{c_k \beta_{K2} \xi_2}{N} & \frac{c_k \beta_{K2} \xi_2 \xi_2}{N} & \ldots & \frac{c_k \beta_{KK} \xi_K}{N} & \frac{c_k \beta_{KK} \xi_K \xi_K}{N}
\end{bmatrix},$$

where $\zeta = p_s (n_1), \xi_m = p_t (m) (n_m)$, and $1 \leq l, m \leq K$.

From the notations defined above, equation (1) can be formulated briefly as

$$\frac{dS(t)}{dt} = -\text{diag}(S(t)) \Phi I(t),$$

$$\frac{dI(t)}{dt} = \text{diag}(S(t)) \Phi I(t) - \text{diag}(\Gamma) I(t),$$

$$\frac{dR(t)}{dt} = \text{diag}(\Gamma) I(t),$$

with initial conditions $S(0) > 0, I(0) \geq 0, R(0) = 0$.

According to the basic existence, uniqueness and continuation results of solutions in [10] and positivity properties of solutions in [32], it is not difficult to obtain the global existence, nonnegative of the solution of system (1) with the initial values (2), which is shown as below in Proposition 1.

**Proposition 1.** Given the initial conditions (2), system (1) admits a unique solution

$$\begin{bmatrix} S_u^{(1)}(t), I_u^{(1)}(t), S_v^{(1)}(t), I_v^{(1)}(t), \ldots, S_u^{(K)}(t), I_u^{(K)}(t), S_v^{(K)}(t), I_v^{(K)}(t), R(t) \end{bmatrix}^T,$$

which exits on $[0, \infty)$ and maintains nonnegativity all the time.
Note that Proposition 1 indicates that the feasible region of model (1) with the initial distributions (2) is
\[
\Omega = \left\{ \begin{array}{l}
S_u^{(1)}(t), I_u^{(1)}(t), S_v^{(1)}(t), I_v^{(1)}(t), \ldots,
S_u^{(K)}(t), I_u^{(K)}(t), S_v^{(K)}(t), I_v^{(K)}(t), R(t) \end{array} \right\}^T \in \mathbb{R}^{4K+1}:
\sum_{l=1}^K \left( S_u^{(l)}(t) + I_u^{(l)}(t) + S_v^{(l)}(t) + I_v^{(l)}(t) \right) + R(t) \equiv N - \sum_{l=1}^K V_0^{(l)} \right\},
\]

3.1. The final size. The final size of the epidemic is defined as the number of susceptible persons who actually acquire the disease during the course of the epidemic [21], which is a very concerned issue for public health authorities. Kermack and McKendrick first studied the final epidemic size based on a SIR model with homogeneous mixing [15]. Since then, a range of researchers investigated the final size problem by developing various epidemic model with heterogeneous mixing patterns (see [1, 3, 5, 19, 20, 26] and references therein). By applying the similar classic approach as in [21], we will first obtain the final size equation for a multi-group SIR model with proportionate mixing and group-specific fractionated vaccination, and then prove that a unique value of the final size is determined by the final size equation.

In the l-th group, it follows from system (1) that both \( S_u^{(l)}(t) \) and \( S_v^{(l)}(t) \) are nonincreasing with time \( t \), and the total number of individuals in each subpopulation is preserved, which indicates that \( 0 \leq S_u^{(l)}(t) \leq N_0^{(l)}, 0 \leq S_v^{(l)}(t) \leq N_0^{(l)} \). Thus, \( S_u^{(l)}(\infty) := \lim_{t \to \infty} S_u^{(l)}(t) \) and \( S_v^{(l)}(\infty) := \lim_{t \to \infty} S_v^{(l)}(t) \) exist. According the definition [21], the final size of the l-th group and total population are represented as \( S_u^{(l)}+I_u^{(l)}+I_v^{(l)}-S_u^{(l)}(\infty)-S_v^{(l)}(\infty) = S_u^{(l)}+I_u^{(l)}+I_v^{(l)}-S_u^{(l)}(\infty)-S_v^{(l)}(\infty) = N_0^{(l)}-V_0^{(l)}-S_u^{(l)}(\infty)-S_v^{(l)}(\infty) \) and \( \sum_{l=1}^K \left( N_0^{(l)}-V_0^{(l)}-S_u^{(l)}(\infty)-S_v^{(l)}(\infty) \right) \) respectively. Similarly, it is easy to show that \( R(\infty) := \lim_{t \to \infty} R(t) \) exists. Moreover, the existence of \( I_u^{(l)}(\infty) \) and \( I_v^{(l)}(\infty) \) are proved in Lemma 3.1.

Lemma 3.1. For model (1) with the initial conditions (2), \( I_u^{(l)}(\infty) := \lim_{t \to \infty} I_u^{(l)}(t) \) and \( I_v^{(l)}(\infty) := \lim_{t \to \infty} I_v^{(l)}(t) \) exist, and \( I_u^{(l)}(\infty) = I_v^{(l)}(\infty) = 0 \) for \( l = 1, \ldots, K \).

Proof. Integrating the R-equation of model (1) from 0 to \( t \), we obtain
\[
R(t) = \sum_{l=1}^K \left( \gamma_l \int_0^t I_u^{(l)}(s)ds + \gamma_p I_u^{(l)}(t) + \gamma_r I_u^{(l)}(t) \right) \int_0^t I_v^{(l)}(s)ds .
\]

Recall that \( R(\infty) \) exists, \( I_u^{(l)}(t) \) and \( I_v^{(l)}(t) \) are nonnegative for any positive integer \( 1 \leq l \leq K \) and the derivatives of \( I_u^{(l)}(t) \) and \( I_v^{(l)}(t) \) are continuous and bounded for all \( t \geq 0 \). Hence \( I_u^{(l)}(\infty) \) and \( I_v^{(l)}(\infty) \) exits. Furthermore, it is easy to see that for all initial conditions, \( I_u^{(l)}(\infty) = I_v^{(l)}(\infty) = 0 \). This completes the proof of this lemma.

It clearly follows from Lemma 3.1 that \( \mathbf{I}(\infty) = 0_{2K} \), where
\[
\mathbf{I}(\infty) = \begin{bmatrix} I_u^{(1)}(\infty), I_v^{(1)}(\infty), \ldots, I_u^{(K)}(\infty), I_v^{(K)}(\infty) \end{bmatrix}^T .
\]
Lemma 3.2. Consider the epidemic system (1) with initial conditions (2). The final size equations for \( S_u^{(l)}(\infty) \) and \( S_v^{(l)}(\infty) \) are given by

\[
S_u^{(l)}(\infty) = S_{u0}^{(l)} \cdot \exp \left( \sum_{m=1}^{K} \frac{c_m \beta_{lm} }{N \gamma_m} \left( S_u^{(m)}(\infty) - S_u^{(m)}(0) - I_u^{(m)}(0) \right) \right)
\]

and

\[
S_v^{(l)}(\infty) = S_{v0}^{(l)} \cdot \exp \left( \sum_{m=1}^{K} \frac{c_m \beta_{lm} P_i^{(m)} \varepsilon_i^{(m)} (n_m)}{N \gamma_m \rho_r^{(m)} \varepsilon_r^{(m)} (n_m)} \left( S_v^{(m)}(\infty) - S_v^{(m)}(0) - I_v^{(m)}(0) \right) \right),
\]

where \( l = 1, \ldots, K \).

Remark 2. In Lemma 3.2, we adopt the classic approach to derive the final size equations, as provided in many references (see [3, 5, 20, 21]). Interested readers can refer to the Appendix A for the detailed proof of Lemma 3.2.

Recall the compact form of system (1), namely equation (3), we can rewrite the final size equations into the following concise form:

\[
S(\infty) = \exp \left( \text{diag} \left( \Phi \text{diag} (I)^{-1} (S(\infty) - S(0) - I(0)) \right) \right) S(0),
\]

where

\[
S(\infty) = \left[ S_u^{(1)}(\infty), S_v^{(1)}(\infty), \ldots, S_u^{(K)}(\infty), S_v^{(K)}(\infty) \right]^T.
\]

Then it is reasonable to define a map \( M: \mathbb{R}^{2K} \to \mathbb{R}^{2K} \) based on equation (6),

\[
M(Y) = \exp \left( \text{diag} \left( \Phi \text{diag} (I)^{-1} (Y - S(0) - I(0)) \right) \right) S(0),
\]

where

\[
M(Y) = [M_1(Y), \ldots, M_{2K}(Y)]^T,
\]

\[
Y = [Y_1, \ldots, Y_{2K}]^T \in \mathbb{R}^{2K},
\]

\[
M_{2l-1}(Y) = S_{u0}^{(l)} \cdot \exp \left( \sum_{m=1}^{K} \frac{c_m \beta_{lm} }{N \gamma_m} (Y_{2m-1} - S_u^{(m)}(0) - I_u^{(m)}(0)) \right)
\]

\[
+ \sum_{m=1}^{K} \frac{c_m \beta_{lm} P_i^{(m)} \varepsilon_i^{(m)} (n_m)}{N \gamma_m \rho_r^{(m)} \varepsilon_r^{(m)} (n_m)} (Y_{2m} - S_v^{(m)}(0) - I_v^{(m)}(0)),
\]

Note that Lemma 3.1 indicates that \( R(\infty) = N - \sum_{l=1}^{K} V_0^{(l)} - \sum_{l=1}^{K} S_u^{(l)}(\infty) - \sum_{l=1}^{K} S_v^{(l)}(\infty) \) can be determined if \( S_u^{(l)}(\infty) \) and \( S_v^{(l)}(\infty) \) are uniquely determined for \( l = 1, \ldots, K \). In Lemma 3.2, we establish the final size equation of epidemics involving \( S_u^{(l)}(\infty) \) and \( S_v^{(l)}(\infty) \) for all \( l \in \{1, \ldots, K\} \).
and indicates that \( M \) admits a unique fixed point. Indeed, via the induction method, we have

It then follows that implies that

Theorem 3.3. For model (1) to compute the final size.

is summarized in Theorem 3.3, which also provides a possible numerical algorithm

By employing analogous method in [21, Theorem 4.4], we obtain that a fixed point

point \( S \) of \( M \) of

The basic reproduction number, \( R \), is determined as the next generation matrix \([33]\) to compute \( R \). Under the vaccination programs, we are going to derive this index, which can also be called the control reproduction number when control strategies are applied. Denote

\[
M_{2l}(Y) = S_v^{(l)} \cdot \exp \left( \sum_{m=1}^{K} \frac{c_m \beta_l m^{(m)} \pi_{l}(m)}{N_m} \left( Y_{2m-1} - S_{u0}^{(m)} - I_{u0}^{(m)} \right) \right)
\]

\[
+ \sum_{m=1}^{K} \frac{c_m \beta_l m^{(m)} \pi_{l}(m)}{N_m p_r^{(m)} \pi_{r}(m)} \left( \left( Y_{2m} - S_{u0}^{(m)} - I_{u0}^{(m)} \right) \right),
\]

and

\[
1 \leq l \leq K.
\]

It follows from Lemma 3.2 that the final size is uniquely determined if \( M(Y) \) admits a unique fixed point. Indeed, \( M(Y) \) is monotonically increasing, which indicates that \( 0_{2K} \leq M(S(0)) \leq S(0) \), where \( S(0) \geq 0_{2K} \) and \( I(0) \geq 0_{2K} \). By virtue of induction method, we have

\[
0_{2K} \leq M(0_{2K}) \leq \cdots \leq M^n(0_{2K}) \leq M^{n+1}(0_{2K})
\]

\[
\leq M^{n+1}(S(0)) \leq \cdots \leq M(S(0)) \leq S(0).
\]

It then follows that \( 0_{2K} \leq \lim_{n \to \infty} M^n(0_{2K}) \leq \lim_{n \to \infty} M^n(S(0)) \leq S(0) \), which implies that \( M \) admits all possible fixed points in

\[
\left[ \lim_{n \to \infty} M^n(0_{2K}), \lim_{n \to \infty} M^n(S(0)) \right].
\]

By employing analogous method in [21, Theorem 4.4], we obtain that a fixed point of \( M \), \( S(\infty) \), exists uniquely in \( [0_{2K}, S(0)] \). The detailed conclusion of the final size is summarized in Theorem 3.3, which also provides a possible numerical algorithm to compute the final size.

**Theorem 3.3.** For model (1) with the initial values (2), \( M \) exists a unique fixed point \( S(\infty) \) in \( [0_{2K}, S(0)] \) and \( S(\infty) \) can be determined differently on different initial conditions:

1. If \( S(0) \gg 0_{2K} \) and \( I(0) > 0_{2K} \), then \( S(\infty) = \lim_{n \to \infty} M^n(0_{2K}) \),

2. If \( S(0) \gg 0_{2K} \) and \( I(0) \geq 0_{2K} \), then \( S(\infty) = \lim_{n \to \infty} M^n(S(0)) \).

3.2. The basic reproduction number. The basic reproduction number, \( R_0 \), serving as a threshold parameter, describes the average of all the secondary infections caused by a single randomly selected infective one over the course of his or her infection period [33]. In this subsection, we adopt the classic method of next generation matrix [33] to compute \( R_0 \). Under the vaccination programs, we are going to derive this index, which can also be called the control reproduction number when control strategies are applied. Denote

\[
x = \begin{bmatrix} x_1, & x_2, & \ldots, & x_{2K-1}, & x_{2K}, & x_{2K+1}, & x_{2K+2}, & \ldots, & x_{4K-1}, & x_{4K}, & x_{4K+1} \end{bmatrix}^T
\]

\[
= \begin{bmatrix} I_u^{(1)}, & I_v^{(1)}, & \ldots, & I_u^{(K)}, & I_v^{(K)}, & S_u^{(1)}, & S_v^{(1)}, & \ldots, & S_u^{(K)}, & S_v^{(K)}, & R \end{bmatrix}^T.
\]
Denote $\mathcal{F}(x)$ as the distribution of the rate of the new infection, and $\mathcal{V}(x)$ as the distribution of the rate of transition:

$$
\mathcal{F}(x) = \left[ \mathcal{F}_1(x), \mathcal{F}_2(x), \ldots, \mathcal{F}_{2K-1}(x), \mathcal{F}_{2K}(x), \right]^T
$$

$$
\mathcal{F}_{2K+1}(x), \mathcal{F}_{2K+2}(x), \ldots, \mathcal{F}_{4K-1}(x), \mathcal{F}_{4K}(x), \mathcal{F}_{4K+1}(x)\right]^T
$$

$$
\mathcal{F}_{2K+1}(x), \mathcal{F}_{2K+2}(x), \ldots, \mathcal{F}_{4K-1}(x), \mathcal{F}_{4K}(x), \mathcal{F}_{4K+1}(x)\right]^T
$$

$$
\begin{bmatrix}
F^{(1)}_{UI}, & F^{(1)}_{VI}, & \ldots, & F^{(K)}_{UI}, & F^{(K)}_{VI}, & 0, & 0, & \ldots, & 0, & 0, & 0
\end{bmatrix}^T,
$$

and

$$
\mathcal{V}(x) = \left[ \mathcal{V}_1(x), \mathcal{V}_2(x), \ldots, \mathcal{V}_{2K-1}(x), \mathcal{V}_{2K}(x), \right]^T
$$

$$
\mathcal{V}_{2K+1}(x), \mathcal{V}_{2K+2}(x), \ldots, \mathcal{V}_{4K-1}(x), \mathcal{V}_{4K}(x), \mathcal{V}_{4K+1}(x)\right]^T
$$

$$
\begin{bmatrix}
F^{(1)}_{UR}, & F^{(1)}_{VR}, & \ldots, & F^{(K)}_{UR}, & F^{(K)}_{VR}, & F^{(1)}_{UI}, & F^{(1)}_{VI}, & \ldots, & F^{(K)}_{UI}, & F^{(K)}_{VI}, & -F_R
\end{bmatrix}^T
$$

where

$$
F^{(l)}_{UI} = \sum_{m=1}^{K} \frac{c_l \beta_l m}{N} \left( I_u^m + P_l n_r \right) S_u^l,
$$

$$
F^{(l)}_{VI} = \sum_{m=1}^{K} \frac{c_l \beta_l m}{N} \left( I_u^m + P_l n_r \right) S_v^l,
$$

$$
F^{(l)}_{UR} = \gamma_l I_u^l, \quad F^{(l)}_{VR} = \gamma_l \rho_r n_l I_v^l,
$$

with $l = 1, \ldots, K$.

Through a simple computation, one can obtain the following disease free equilibrium of model (1) with initial condition (2)

$$
\tilde{S}(0) = \left[ S_{u0}^{(1)}, 0, S_{v0}^{(1)}, 0, \ldots, S_{u0}^{(K)}, 0, S_{v0}^{(K)}, 0, 0 \right]^T
$$

with $S_{u0}^{(l)}$ and $S_{v0}^{(l)}$ being evaluated from the initial condition (2) with $S_0^{(l)} = N_0^{(l)}$ for $0 \leq l \leq K$. Following the idea in [33, Lemma 1] and linearizing the system at the disease-free equilibrium, the matrices $\mathcal{F}$ and $\mathcal{V}$ can be given below:

$$
\mathcal{F} = \left[ \frac{\partial \mathcal{F}_q}{\partial x_w} \left( \tilde{S}(0) \right) \right] = \text{diag} \left( \tilde{S}(0) \right) \Phi,
$$

and

$$
\mathcal{V} = \left[ \frac{\partial \mathcal{V}_q}{\partial x_w} \left( \tilde{S}(0) \right) \right] = \text{diag} \left( \Gamma \right),
$$

where $q, w = 1, \ldots, 2K$. Then, the next generation matrix is:

$$
\mathcal{F} \mathcal{V}^{-1} = \text{diag} \left( \tilde{S}(0) \right) \Phi \text{diag} \left( \Gamma \right)^{-1}.
$$
Therefore, the basic reproduction number of system (1) with the initial conditions (2) is
\[
\mathcal{R}_0 = \rho (\mathcal{FV}^{-1}) = \rho \left( \text{diag} \left( \tilde{S}(0) \right) \Phi \text{diag} (I)^{-1} \right),
\]
where \( \rho (\mathcal{FV}^{-1}) \) denotes the spectral radius of the next generation matrix \( \mathcal{FV}^{-1} \).

3.3. Relationship between the final size and \( \mathcal{R}_0 \). We have already obtained the results of the final size and the basic reproduction number of model (1) with the initial values (2). Based on these results, it is necessary to reveal the relationship between the final size and the basic reproduction number \( \mathcal{R}_0 \). In this subsection we only consider the final size relations with \( \mathcal{R}_0 \) in the case of \( \Phi > 0_{2K \times 2K} \) and \( \Phi \) is irreducible. It is easy to check either when the case \( \Phi \gg 0_{2K \times 2K} \) or the case \( c_l > 0 \) and \( \beta_{lm} > 0 \) for all \( 1 \leq l, m \leq K \) is sufficient since any positive matrix is irreducible.

We first observe that equation (14) in company with equation (16) can be rewritten as
\[
\ln S(t) - \ln S(0) = \Phi \text{diag} (I)^{-1} (S(t) + I(t) - S(0) - I(0)),
\]
where
\[
\ln S(t) = \left[ \ln S_u^{(1)}(t), \ln S_u^{(1)}(t), \ldots, \ln S_u^{(K)}(t), \ln S_v^{(K)}(t) \right]^T,
\]
and
\[
\ln S(0) = \left[ \ln S_u^{(1)}(0), \ln S_u^{(1)}(0), \ldots, \ln S_u^{(K)}(0), \ln S_v^{(K)}(0) \right]^T.
\]
Subsequently, letting \( t \) goes to \( \infty \) in equation (7) and noticing that \( I(\infty) = 0_{2K} \), we obtain
\[
\ln S(\infty) - \ln S(0) = \Phi \text{diag} (I)^{-1} (S(\infty) - S(0) - I(0)),
\]
where
\[
\ln S(\infty) = \left[ \ln S_u^{(1)}(\infty), \ln S_u^{(1)}(\infty), \ldots, \ln S_u^{(K)}(\infty), \ln S_v^{(K)}(\infty) \right]^T.
\]
Just note that \( \text{diag} \left( \tilde{S}(0) \right) \Phi \text{diag} (I)^{-1} = \mathcal{FV}^{-1} \). Therefore, multiplying equation (8) by \( \text{diag} \left( \tilde{S}(0) \right) \), one gets
\[
\text{diag} \left( \tilde{S}(0) \right) \left( \ln S(\infty) - \ln S(0) \right) = \mathcal{FV}^{-1} (S(\infty) - S(0) - I(0)).
\]
It is easy to see that \( \mathcal{FV}^{-1} \) is irreducible since \( \Phi \gg 0_{2K \times 2K} \) is irreducible and \( \mathcal{FV}^{-1} = \text{diag} \left( \tilde{S}(0) \right) \Phi \text{diag} (I)^{-1} \). Additionally, by Perron–Frobenius theorem, there exits a left row vector
\[
0_{1 \times 2K} \preccurlyeq Z = \left[ Z_1, \ldots, Z_{2K} \right] \in \mathbb{R}^{1 \times 2K},
\]
with eigenvalue \( \mathcal{R}_0 \), such that
\[
Z \text{diag} \left( \tilde{S}(0) \right) \left( \ln S(\infty) - \ln S(0) \right) = \mathcal{R}_0 Z (S(\infty) - S(0) - I(0)),
\]
which gives the final size relation with \( \mathcal{R}_0 \).
3.4. Infection attack rate (IAR). Infection attack rate (IAR) is defined as the proportion of susceptible individuals who are ultimately infected during the course of an epidemic. This is another critical issue in assessing the size of the epidemic. According to the definition, IAR for unvaccinated, vaccinated and total populations in l-th (1 \leq l \leq K) group, denoted as \( \mathcal{IAR}_u^{(l)} \), \( \mathcal{IAR}_v^{(l)} \) and \( \mathcal{IAR}^{(l)} \) respectively, are shown as follows:

\[
\mathcal{IAR}_u^{(l)} = \frac{S_u^{(l)} + I_u^{(l)} - S_u^{(l)}(\infty)}{S_u^{(l)} + I_u^{(l)}} = 1 - \frac{S_u^{(l)}(\infty)}{S_u^{(l)} + I_u^{(l)}} = 1 - \frac{S_u^{(l)}}{S_u^{(l)} + I_u^{(l)}} \cdot \exp \left( - \sum_{m=1}^{K} \frac{c_m \beta_{lm} (m)}{N \gamma_m} \left( S_u^{(m)} + I_u^{(m)} \right) \right) \mathcal{IAR}_u^{(m)}
\]

\[
\mathcal{IAR}_v^{(l)} = \frac{S_v^{(l)} + I_v^{(l)} - S_v^{(l)}(\infty)}{S_v^{(l)} + I_v^{(l)}} = 1 - \frac{S_v^{(l)}(\infty)}{S_v^{(l)} + I_v^{(l)}} = 1 - \frac{S_v^{(l)}}{S_v^{(l)} + I_v^{(l)}} \cdot \exp \left( - \sum_{m=1}^{K} \frac{c_m \beta_{lm} p_s (m) \varepsilon_s (n_m)}{N \gamma_m} \left( S_v^{(m)} + I_v^{(m)} \right) \right) \mathcal{IAR}_v^{(m)}
\]

\[
\mathcal{IAR}_u^{(m)} = \mathcal{IAR}_v^{(m)} - \sum_{m=1}^{K} \frac{c_m \beta_{lm} p_r (m) \varepsilon_r (n_m)}{N \gamma m} \left( S_v^{(m)} + I_v^{(m)} \right) \mathcal{IAR}_v^{(m)}
\]

and

\[
\mathcal{IAR}^{(l)} = \frac{S_u^{(l)} + I_u^{(l)} + S_v^{(l)} + I_v^{(l)} - S_u^{(l)}(\infty) - S_v^{(l)}(\infty)}{S_u^{(l)} + I_u^{(l)} + S_v^{(l)} + I_v^{(l)}} = 1 - \frac{S_u^{(l)}(\infty) + S_v^{(l)}(\infty)}{S_u^{(l)} + I_u^{(l)} + S_v^{(l)} + I_v^{(l)}} = 1 - \frac{S_u^{(l)} + S_v^{(l)}}{S_u^{(l)} + I_u^{(l)} + S_v^{(l)} + I_v^{(l)}} \cdot \exp \left( - \sum_{m=1}^{K} \frac{c_m \beta_{lm} (m)}{N \gamma_m} \left( S_u^{(m)} + I_u^{(m)} \right) \right) \mathcal{IAR}_u^{(m)}
\]

\[
\mathcal{IAR}_u^{(m)} = \mathcal{IAR}_v^{(m)} - \sum_{m=1}^{K} \frac{c_m \beta_{lm} p_s (m) \varepsilon_s (n_m)}{N \gamma m} \left( S_v^{(m)} + I_v^{(m)} \right) \mathcal{IAR}_v^{(m)}
\]

\[
\mathcal{IAR}_u^{(m)} - \sum_{m=1}^{K} \frac{c_m \beta_{lm} p_r (m) \varepsilon_r (n_m)}{N \gamma m} \left( S_v^{(m)} + I_v^{(m)} \right) \mathcal{IAR}_v^{(m)}
\]

In addition, IAR for total unvaccinated, total vaccinated and the whole populations, denoted as \( \mathcal{IAR}_u \), \( \mathcal{IAR}_v \) and \( \mathcal{IAR} \) respectively, the formulations of which
are shown as below:

\[
\mathcal{IAR}_u = \frac{\sum_{l=1}^{K} (S_{u0}^{(l)} + I_{u0}^{(l)}) - \sum_{l=1}^{K} S_{u}^{(l)}(\infty)}{\sum_{l=1}^{K} (S_{u0}^{(l)} + I_{u0}^{(l)})} = 1 - \frac{\sum_{l=1}^{K} S_{u}^{(l)}(\infty)}{\sum_{l=1}^{K} (S_{u0}^{(l)} + I_{u0}^{(l)})}
\]

\[
= 1 - \frac{1}{\sum_{l=1}^{K} (S_{u0}^{(l)} + I_{u0}^{(l)})} \sum_{l=1}^{K} S_{u0}^{(l)} \cdot \exp \left( - \sum_{m=1}^{K} c_m \beta_{lm} \frac{(m)}{N\gamma_m} \left( S_{v0}^{(m)} + I_{v0}^{(m)} \right) \mathcal{IAR}_v^{(m)} \right),
\]

\[
\mathcal{IAR}_v = \frac{\sum_{l=1}^{K} (S_{v0}^{(l)} + I_{v0}^{(l)}) - \sum_{l=1}^{K} S_{v}^{(l)}(\infty)}{\sum_{l=1}^{K} (S_{v0}^{(l)} + I_{v0}^{(l)})} = 1 - \frac{\sum_{l=1}^{K} S_{v}^{(l)}(\infty)}{\sum_{l=1}^{K} (S_{v0}^{(l)} + I_{v0}^{(l)})}
\]

\[
= 1 - \frac{1}{\sum_{l=1}^{K} (S_{v0}^{(l)} + I_{v0}^{(l)})} \sum_{l=1}^{K} S_{v0}^{(l)} \cdot \exp \left( - \sum_{m=1}^{K} c_m \beta_{lm} \frac{(m)}{N\gamma_m} \left( S_{v0}^{(m)} + I_{v0}^{(m)} \right) \mathcal{IAR}_u^{(m)} \right),
\]

and

\[
\mathcal{IAR} = \frac{\sum_{l=1}^{K} (S_{u0}^{(l)} + I_{u0}^{(l)} + S_{v0}^{(l)} + I_{v0}^{(l)} - S_{u}^{(l)}(\infty) - S_{v}^{(l)}(\infty))}{\sum_{l=1}^{K} (S_{u0}^{(l)} + I_{u0}^{(l)} + S_{v0}^{(l)} + I_{v0}^{(l)})}
\]

\[
= 1 - \frac{\sum_{l=1}^{K} S_{u}^{(l)}(\infty)}{\sum_{l=1}^{K} (S_{u0}^{(l)} + I_{u0}^{(l)} + S_{v0}^{(l)} + I_{v0}^{(l)})} - \frac{\sum_{l=1}^{K} S_{v}^{(l)}(\infty)}{\sum_{l=1}^{K} (S_{u0}^{(l)} + I_{u0}^{(l)} + S_{v0}^{(l)} + I_{v0}^{(l)})}
\]
for the sake of researching fractional-dose influenza vaccine reasonably, we adjust 60 years either have not been studied or have a diminished response. Therefore, case of influenza vaccine shortage since people younger than 18 years or older than vaccination should be administered only to healthy adults under the age of 60 in nation is considered [18]. What’s more, results in [35] suggest that reduced-dose 4.1. Parameter fitting. Longini et. al consider that, in absence of vaccination, the population is divided into four age groups with different attack rates and the simulation result shows that children have the highest ones (about 56%) [18]. Authors in [18] calculate the basic reproduction number of \( R_0 = 1.68 \) with their model and they assume that the initial infective persons are unvaccinated when vaccination is considered [18]. What’s more, results in [35] suggest that reduced-dose vaccination should be administered only to healthy adults under the age of 60 in case of influenza vaccine shortage since people younger than 18 years or older than 60 years either have not been studied or have a diminished response. Therefore, for the sake of researching fractional-dose influenza vaccine reasonably, we adjust

\[
1 - \frac{1}{S_{u0}^{(l)} + I_{u0}^{(l)} + S_{e0}^{(l)} + I_{e0}^{(l)}} \sum_{m=1}^{K} \left( \frac{c_m \beta_{lm}}{N \gamma_m} \right) \exp \left( - \frac{1}{K} \sum_{i=1}^{K} \left( S_{u0}^{(l)} + I_{u0}^{(l)} + S_{e0}^{(l)} + I_{e0}^{(l)} \right) \right) \]

\[
\left( S_{e0}^{(m)} + I_{e0}^{(m)} \right) \mathcal{IAR}_{u}^{(m)} - \frac{K}{\sum_{l=1}^{K} \left( S_{u0}^{(l)} + I_{u0}^{(l)} + S_{e0}^{(l)} + I_{e0}^{(l)} \right) \mathcal{IAR}_{u}^{(m)}} \left( \frac{c_m \beta_{lm} p_i^{(m)} \varepsilon_i^{(m)} (n_m)}{N \gamma_m p_r^{(m)} \varepsilon_r^{(m)} (n_m)} \right) \left( S_{e0}^{(m)} + I_{e0}^{(m)} \right) \mathcal{IAR}_{v}^{(m)} \right).
\]

\[
= \sum_{m=1}^{K} \frac{c_m \beta_{lm} p_s^{(m)} \varepsilon_s^{(m)} (n_m)}{N \gamma_m p_r^{(m)} \varepsilon_r^{(m)} (n_m)} \left( S_{s0}^{(m)} + I_{s0}^{(m)} \right) \mathcal{IAR}_{u}^{(m)}
\]

\[
= \sum_{m=1}^{K} \frac{c_m \beta_{lm} p_s^{(m)} \varepsilon_s^{(m)} (n_m)}{N \gamma_m p_r^{(m)} \varepsilon_r^{(m)} (n_m)} \left( S_{s0}^{(m)} + I_{s0}^{(m)} \right) \mathcal{IAR}_{u}^{(m)}
\]

\[
+ \sum_{m=1}^{K} \frac{c_m \beta_{lm} p_s^{(m)} \varepsilon_s^{(m)} (n_m) \mathcal{IAR}_{u}^{(m)} \varepsilon_r^{(m)} (n_m)}{N \gamma_m p_r^{(m)} \varepsilon_r^{(m)} (n_m)} \left( S_{e0}^{(m)} + I_{e0}^{(m)} \right) \mathcal{IAR}_{v}^{(m)}
\]

\[
= \sum_{m=1}^{K} \frac{c_m \beta_{lm} p_s^{(m)} \varepsilon_s^{(m)} (n_m) \mathcal{IAR}_{u}^{(m)} \varepsilon_r^{(m)} (n_m)}{N \gamma_m p_r^{(m)} \varepsilon_r^{(m)} (n_m)} \left( S_{e0}^{(m)} + I_{e0}^{(m)} \right) \mathcal{IAR}_{v}^{(m)}
\]

It is worth noting that the final size, \( R_0 \) and the IAR are strongly related to the group-specific fractional vaccine efficacy. In the following section, numerical simulations involving multiple groups of susceptible and infected individuals and the fractional-dose vaccine related characteristics are performed to investigate the influences of group-specific fractional-dose vaccines on disease control and prevention.

4. Numerical simulations. To apply the model to realistic example, we study the 1957–1958 Asian influenza pandemic that was caused by influenza A virus (H2N2) as reported in Longini et al [18]. Since viruses of the H2 subtype continue to infect avian species and pigs, the threat of reintroduction into humans remains [14]. Much of the world’s population lacks any pre-existing immunity to the H2N2 viruses that circulated 50-60 years ago, and the majority of people alive today would have no immunity to H2 influenza viruses if viruses of this subtype began circulating in the human population again [27]. In this section, we conduct a case study of 1957–1958 Asian influenza pandemic caused by influenza virus (H2N2), to investigate the impact of fractionated vaccination on disease control [18]. Influenza associated parameters are first fitted. Then, we explore the most effective strategies when all the vaccines are administrated only in standard-dose. Finally, we evaluate the feasibility of dose-sparing campaign, and discuss the sensitivity of final size and IAR with respect to the five fractionated vaccines related parameters \( \varepsilon_j^{(l)} (n_l) \) for \( l \in \mathbb{Z}^+ \) and \( j = e, f, i, s, r \).

4.1. Parameter fitting. Longini et. al consider that, in absence of vaccination, the population is divided into four age groups with different attack rates and the simulation result shows that children have the highest ones (about 56%) [18]. Authors in [18] calculate the basic reproduction number of \( R_0 = 1.68 \) with their model and they assume that the initial infective persons are unvaccinated when vaccination is considered [18]. What’s more, results in [35] suggest that reduced-dose vaccination should be administered only to healthy adults under the age of 60 in case of influenza vaccine shortage since people younger than 18 years or older than 60 years either have not been studied or have a diminished response. Therefore, for the sake of researching fractional-dose influenza vaccine reasonably, we adjust
the entire population of 2,000 persons to three groups and use the parameters and initial values as listed in Table 3 for the influenza pandemic.

Table 3. Data of parameters and variables

| Symbol | Description                                | Value | Unit    | Reference |
|--------|--------------------------------------------|-------|---------|-----------|
| $N$    | Total population                           | 2,000 | Individuals | Estimated |
| $N_0^{(1)}$ | Children aged 0–17 years (group 1)     | 580   | Individuals | Estimated |
| $N_0^{(2)}$ | Young adults aged 18–60 years (group 2) | 1170  | Individuals | Estimated |
| $N_0^{(3)}$ | Older adults aged more than 60 years (group 3) | 250  | Individuals | Estimated |
| $S_0^{(1)}$ | Susceptible persons in group 1          | 577   | Individuals | Estimated |
| $S_0^{(2)}$ | Susceptible persons in group 2          | 1163  | Individuals | Estimated |
| $S_0^{(3)}$ | Susceptible persons in group 3          | 248   | Individuals | Estimated |
| $I_0^{(1)}$ | Infected persons in group 1            | 3     | Individuals | [24]    |
| $I_0^{(2)}$ | Infected persons in group 2            | 7     | Individuals | [24]    |
| $I_0^{(3)}$ | Infected persons in group 3            | 2     | Individuals | [24]    |
| $p$    | Vaccine coverage for the total population | variable | Dimensionless | Estimated |
| $\gamma$ | Average recover rate for overall population ($\gamma_l = \gamma$ for $l = 1, 2, 3$) | $1/4.1$ days$^{-1}$ | \[18\] |

For better adapting parameters, we select average rate of infection in every group, which means that $\beta_1 = \beta_2 = \beta_3 = \beta_l$ for $l = 1, 2, 3$. The estimated values and simulation results are presented in Table 4, where $S_0 = \left( \sum_{l=1}^{3} c_l \beta_l S_0^{(l)} \right) / (N\gamma)$.

Note that the simulation results of IAR and $R_0$ are slightly different from those in [18] due to the differences in model structures. The authors used stochastic epidemic simulations to investigate the effectiveness of targeted antiviral prophylaxis to contain influenza in [18]. The following numerical simulations are based on the parameters and initial values in Tables 3 and 4.

4.2. Optimization on vaccine distribution. In this subsection, we study how vaccination effects vary with different vaccine distributions and establish the most effective vaccine distribution scheme under the standard-dose only vaccination policy.
Table 4. List of estimated values and simulation results

| Symbol | Value | Unit       |
|--------|-------|------------|
| $c_1$  | 7     | Dimensionless |
| $c_2$  | 5     | Dimensionless |
| $c_3$  | 3     | Dimensionless |
| $\beta_1$ | 0.098 | Dimensionless |
| $\beta_2$ | 0.037 | Dimensionless |
| $\beta_3$ | 0.064 | Dimensionless |
| $IAR^{(1)}$ | 59%  | Dimensionless |
| $IAR^{(2)}$ | 29%  | Dimensionless |
| $IAR^{(3)}$ | 45%  | Dimensionless |
| $\mathcal{R}_0$ | 40%  | Dimensionless |
| $\mathcal{R}_0$ | 1.35 | Dimensionless |

In this case, the explicit formula for the basic reproduction number $\mathcal{R}_0$ is

$$\mathcal{R}_0 = \frac{\sum_{i=1}^{3} \left( c_i \beta_i S_{u0}^{(i)} + c_i \beta_i p_i^{(i)} S_{w0}^{(i)} / p_r^{(i)} \right)}{N\gamma}.$$

For the case study, we assume that the constant parameters used are as exhibited in Table 5 according to [16, 18].

Table 5. Definition of the constant parameters

| Symbol | Value | Unit       | Reference |
|--------|-------|------------|-----------|
| $p_e^{(1)}$ | 0.75 | Dimensionless | Estimated |
| $p_e^{(2)}$ | 0.79 | Dimensionless | [16]       |
| $p_e^{(3)}$ | 0.77 | Dimensionless | Estimated |
| $p_i^{(1)}$ | 0.59 | Dimensionless | Estimated |
| $p_i^{(2)}$ | 0.63 | Dimensionless | Estimated |
| $p_i^{(3)}$ | 0.61 | Dimensionless | Estimated |
| $p_r^{(1)}$ | 0.67 | Dimensionless | Estimated |
| $p_r^{(2)}$ | 0.65 | Dimensionless | [18]       |
| $p_r^{(3)}$ | 0.66 | Dimensionless | Estimated |
| $p_s^{(1)}$ | 0.57 | Dimensionless | Estimated |
| $p_s^{(2)}$ | 0.55 | Dimensionless | [18]       |
| $p_s^{(3)}$ | 0.56 | Dimensionless | Estimated |
| $p_v^{(1)}$ | 2.3 | Dimensionless | Estimated |
| $p_v^{(2)}$ | 2.5 | Dimensionless | Estimated |
| $p_v^{(3)}$ | 2.4 | Dimensionless | Estimated |

We first compare six indices of control strategies with respect to standard-dose vaccination coverage in seven scenarios which are random vaccination with standard-dose vaccines for only group 1, only group 2, only group 3, groups 1
and 2, groups 1 and 3, groups 2 and 3, and the entire population, respectively. The six indices are, respectively, the basic reproduction number $R_0$, the final size related quantity $\sum_{i=1}^{3} \left( S^{(l)}_u(\infty) + S^{(l)}_v(\infty) \right)$, the outbreak size, the peaking time, the IAR and the number of standard-dose vaccines. Each individual of the target groups in each scenario has the same probability of receiving vaccination. From Fig. 2, vaccinating the entire population is the best strategy for controlling the influenza epidemic but requires more vaccines. Vaccinating groups 1 and 2 has similar effects. Fig. 2(a) shows that $R_0$ could be reduced to less than 1. We can see that $\sum_{i=1}^{3} \left( S^{(l)}_u(\infty) + S^{(l)}_v(\infty) \right)$ is almost the least under the vaccinating the entire population but the IAR is also the least in Figs. 2(b) and 2(e) since $\sum_{i=1}^{3} \left( S^{(l)}_u + I^{(l)}_u + S^{(l)}_v + S^{(l)}_v \right)$ in the case is always the least. Moreover, the outbreak size and the peaking time of the influenza pandemic are controlled at the initial infective scale and the initial time respectively if the standard-dose vaccine coverage for only group 1 (the child group), the most active group, is bigger than 70%, as shown in Figs. 2(c) and 2(d).

Then, to find out the best distribution scheme when the number of influenza vaccines achievable is restricted, we study how the basic reproduction number $R_0$, $\sum_{i=1}^{3} \left( S^{(l)}_u(\infty) + S^{(l)}_v(\infty) \right)$, outbreak size, peaking time and IAR fluctuate in different vaccine distributions as the standard-dose vaccine coverage for the entire population is fixed. There are two vaccine administration policies: one is assigning to one group after another, the other is assigning to one group firstly and then the remaining two groups as a whole or vice versa. In vaccine allocation, the next object is considered until the current target group is fully covered. Each allocation policy has 6 cases. Figs. 3 (g1)–(k1) perform the results of the first policy and Figs. 4 (g2)–(k2) perform the results of the second policy.

Comparing comprehensively, we conclude that three more effective vaccine distributions in containing influenza are first group 1 then group 2 and last group 3, first group 1 then group 3 and last group 2, and first group 1 then groups 2 and 3, respectively. The effects of the three assignments are all better than that of vaccinating the entire population, which are particularly significant when the standard-dose vaccine coverage for the entire population is between 20% and 60%, and the second vaccine administration of the three ones is the best. It implies that first vaccinating the most active group—child group, then the less active group—older adult group, and last the least active group—young adult group is reasonable even though the young adults make up the majority of the entire population. This is consistent with the statement that individuals should be immunized according to the tiered system of priority in times of shortage in Wyatt et al. [35].

4.3. Evaluation of fractional-dose vaccination strategy. Reduced dose has immunogenicity similar to that of standard dose vaccination in healthy individuals less than 60 years old but people younger than 18 years or older than 60 years should not be vaccinated with reduced-dose influenza vaccine because these groups either have not been studied or have a diminished response [35]. Data show that healthy people between the ages of 18 and 60 years have similar immune response to reduced-dose vaccine, suggesting that reduced dosing may be an option to increase the number of immunizations available [35]. In consequence, we research the case of fractional-dose vaccines will be administered to group 2 (young adult group) only
Figure 2. Illustration of the distributions of the basic reproduction number $R_0$ (2(a)), the final size related quantity $\sum_{i=1}^{3} \left( S_u^{(l)}(\infty) + S_v^{(l)}(\infty) \right)$ (2(b)), the outbreak size (2(c)), the peaking time (2(d)), the IAR (2(e)) and the number of vaccines (2(f)) along standard-dose vaccine coverage for different target vaccination groups. In each plot, the red line with square markers indicates scenario 1 (vaccinating only group 1), the red line with asterisk markers scenario 2 (vaccinating only group 2), the green line with diamond markers scenario 3 (vaccinating only group 3), the magenta line with circle markers scenario 4 (vaccinating groups 1 and 2), the blue line with downward-pointing triangle markers scenario 5 (vaccinating groups 1 and 3), the cyan line with upward-pointing triangle markers scenario 6 (vaccinating groups 2 and 3), and the black line with star markers scenario 7 (vaccinating the entire population).
Figure 3. The variations of the basic reproduction number $R_0$ ((g1)), the final size related quantity $\sum_{l=1}^{3} \left( S_u^{(l)}(\infty) + S_v^{(l)}(\infty) \right)$ ((h1)), the outbreak size ((i1)), the peaking time ((j1)), and the IAR ((k1)) over the standard-dose vaccine coverage for the entire population with different vaccine distributions in the first policy. In each plot, the red solid line with plus sign markers indicates the case of first group 1 then group 2 and last group 3, the green dashed line with right-pointing triangle markers the case of first group 1 then group 3 and last group 2, the black dash-dotted line with left-pointing triangle markers the case of first group 2 then group 1 and last group 3, the blue solid line with point markers the case of first group 2 then group 3 and last group 1, the magenta dotted line with six-pointed star markers the case of first group 3 then group 1 and last group 2, the cyan dashed line with cross markers the case of first group 3 then group 2 and last group 1.

with one-fifth dose and standard-dose vaccines be given to the other groups when the number of vaccines is very limited.

Based on the simulation results in the previous subsection, we choose the three optimal vaccine distributions as research objects and study also the five characteristics of the epidemic when 5-fold fractional-dose vaccines are implemented to group
Figure 4. The variations of the basic reproduction number $R_0$ ((g2)), the final size related quantity $\sum_{l=1}^{3} \left( S_u^{(l)}(\infty) + S_v^{(l)}(\infty) \right)$ ((h2)), the outbreak size ((i2)), the peaking time ((j2)), and the IAR ((k2)) with respect to the standard-dose vaccine coverage for the entire population with different vaccine distributions in the second policy. In each plot, the cyan dash-dotted line with upward-pointing triangle markers indicates the case of first groups 1 and 2 and then group 3, the green dotted line with asterisk markers the case of first group 3 and then groups 1 and 2, the red dashed line with square markers the case of first groups 1 and 3 and then group 2, the blue solid line with circle markers the case of first group 2 then groups 1 and 3, the magenta dashed line with downward-pointing triangle markers the case of first groups 2 and 3 and then group 1, the black solid line with diamond markers the case of first group 1 and then groups 2 and 3.

2. We now consider the effects of changing the five parameters $\varepsilon_j^{(2)}(5)$ with $j = e, f, i, s,$ and $r$ on $R_0$, $\sum_{l=1}^{3} \left( S_u^{(l)}(\infty) + S_v^{(l)}(\infty) \right)$, and IAR under the three distributions, respectively, where

$$R_0 = \left( c_1 \beta_1 S_{u0}^{(1)} + c_1 \beta_1 p_s^{(1)} p_r^{(1)} S_{v0}^{(1)} / p_r^{(1)} \right)$$
For convenience, we reduce the five parameters as independent variables to two of the input variables vaccine related parameters on the vaccination impact should be considered.

\[ + c_2 \beta_2 \delta u_0 + c_2 \beta_2 \pi_i(2) \varepsilon_i(5) p_i(2) S_v(2)(5) S_v(0)(2)/ \left( p_i(2) \varepsilon_i(5) \right) \]

\[ + c_3 \beta_3 S_u(0) + c_3 \beta_3 p_i(3) S_v(3)(5) / \left( S_v(3)(5) \right) \cdot (N \gamma) . \]

For sensitivity analysis, we reduce the five parameters as independent variables to two by setting \( \varepsilon(2)_i(5) = \varepsilon(2)_f(5) = \varepsilon(2)_e(5) = \varepsilon(2)_r(5) = \varepsilon(2)_s(5) = \varepsilon(2)_x(5) \in \varepsilon_1, \varepsilon_2 \), where \( \varepsilon_1 = \max\{0, 1/p_r(2)\} \) and \( \varepsilon_2 = \min\{1/p_r(2), 1/p_e(2)\} \). The surfaces in Fig. 6 and Fig. 7, respectively, depict the detailed ranges of values of \( 0, \sum_{i=1}^{3} \left( S_u(2) + S_v(2) \right) \) and IAR with respect to \( \varepsilon(2)_x(5) \) and \( \varepsilon(2)_r(5) \) under first group 1 then group 2 and last group 3 distribution with \( p_1 = 1, p_2 = 0.2, \) and \( p_3 = 0.5 \), first group 1 then group 3 and last group 2 distribution with \( p_1 = 1, p_2 = 0.1, \) and \( p_3 = 1 \), and first group 1 then groups 2 and 3 distribution with \( p_1 = 1, p_2 = p_3 = 0.01 \times 2000/(1170 + 250) \).

From these graphs (i.e., Figs. 5–7), we can see that even under the special assumptions made, the dose fractionation policy in a heterogeneously mixing population is more effective in controlling the influenza epidemic than standard-dose only vaccination strategy in most cases, but there are still a few cases where the fractional-dose vaccine may conversely take negative effects in lowering \( \mathcal{R}_0, \sum_{i=1}^{3} \left( S_u(2) + S_v(2) \right) \) and IAR, which can not be neglected. That is, lower individual doses vaccination for the young adult group is likely to provide extra community-level benefits only when the fractional-dose vaccine efficacy is high enough and it would take negative community-level effects otherwise. This conclusion is valid at least for the sets of parameters used as in Tables 4 and 5 even if the simulation results are highly dependent on the choices of parameters. Note that we have selected the maximal dose fractionation (\( n = 5 \)) to simulate. Therefore, this conclusion still holds and the fractionated dose efficacy benefit threshold becomes more stringent if the fractionation \( n \) is smaller since there is a correspondingly narrower vaccine coverage. Up to this point, further empirical studies for reduced-dose vaccines and fractional-dose vaccination should be required before final fractionated dosing decisions to ensure the robustness of this lower-dose campaign, which was not noted in references [29, 34, 35].

4.4. Sensitivity analysis. When the vaccine stockpiles are insufficient and so fractional-dose strategy is recommended, the effects of changing the five key fractional-dose vaccine related parameters on the vaccination impact should be considered. In this subsection, a global sensitivity analysis is carried out to clarify which one of the input variables \( \varepsilon(2)_x(5), \varepsilon(2)_f(5), \varepsilon(2)_e(5), \varepsilon(2)_r(5), \varepsilon(2)_s(5) \) and \( \varepsilon(2)_r(5) \) is the most influential drivers of \( \sum_{i=1}^{3} \left( S_u(2) + S_v(2) \right) \) and IAR in the three optimal vaccine distributions since the fractional-dose vaccination scheme is only restricted to the young adult group. The baseline values of the five parameters about the young adult group are also set as their average values respectively (i.e., the baseline value of \( \varepsilon(2)_x(5), \varepsilon(2)_f(5), \varepsilon(2)_e(5), \varepsilon(2)_r(5), \) and \( \varepsilon(2)_s(5) \) are, respectively, \( 1/2, 1/2, (1 + p_i(2))/2 \), \( (1 + p_i(2))/2 \), and \( (p_i(2) + 1)/2 \). Following on we explore the effects of changes for \( \sum_{i=1}^{3} \left( S_u(2) + S_v(2) \right) \) and IAR with increase by 10% and decrease by 10% for each baseline value of the five parameters. Then we get simulation results under first group 1 then group 2 and last group 3 assignment with assumption \( p_1 = 1, p_2 = 0.2 \) and \( p_3 = 0.5 \) (see Fig. 8 (t1) and (u1)), under first group 1 then group
Figure 5. Simulations showing the effect of changing $\varepsilon^{(2)}_{i,s}(5)$ and $\varepsilon^{(2)}_{e,f,r}(5)$ on $R_0$ ((q1)), $\sum_{l=1}^{3} \left( S^{(l)}_{u}(\infty) + S^{(l)}_{v}(\infty) \right)$ ((r1)) and IAR ((s1)) when first group 1 then group 2 and last group 3 distribution is carried out. The white lines are contour lines and the black lines are the baselines which stand for corresponding values under the standard-dose only strategy in each subfigure. The values of $p_1$, $p_2$, and $p_3$ are 1, 0.2, and 0.5, respectively.

3 and last group 2 distribution with $p_1 = 1$, $p_2 = 0.1$ and $p_3 = 1$ (see Fig. 8 (t2) and (u2)), under first group 1 then groups 2 and 3 administration with $p_1 = 1$, $p_2 = p_3 = 0.01 \times 2000/(1170 + 250)$ (see Fig. 8 (t3) and (u3)).

The plots in Fig. 8 clearly show that $\sum_{l=1}^{3} \left( S^{(l)}_{u}(\infty) + S^{(l)}_{v}(\infty) \right)$ is most sensitive to $\varepsilon^{(2)}_f(5)$ for all the three distributions. $\varepsilon^{(2)}_{e}(5)$ also has a substantial effect on
Figure 6. Simulations showing the effect of changing \( \varepsilon_{i,s}^{(2)} (5) \) and \( \varepsilon_{e,f,r}^{(2)} (5) \) on \( R_0 \), \( \sum_{l=1}^{3} \left( S_{u}^{(l)} (\infty) + S_{v}^{(l)} (\infty) \right) \), and IAR when first group 1 then group 3 and last group 2 distribution is carried out. The white lines are contour lines and the black lines are the baselines which stand for corresponding values under the standard-dose only strategy in each subfigure. The values of \( p_1, p_2 \) and \( p_3 \) are 1, 0.1 and 1, respectively.

\[
\sum_{l=1}^{3} \left( S_{u}^{(l)} (\infty) + S_{v}^{(l)} (\infty) \right).
\]

Since \( \varepsilon_{i,s}^{(2)} (5) \) and \( \varepsilon_{e,f,r}^{(2)} (5) \) directly determine the number of \( S_{u}^{(2)} \) and \( S_{v}^{(2)} \) and so have main influences on \( S_{u}^{(2)} (\infty) + S_{v}^{(2)} (\infty) \). On the other side, IAR is most sensitive to \( \varepsilon_{i,s}^{(2)} (5) \) because \( \varepsilon_{i,s}^{(2)} (5) \) determines the scale of susceptible subpopulations to acquire the disease. We also note that the effects of \( \varepsilon_{e}^{(2)} (5) \) become significant as the number of vaccines decreases since \( \varepsilon_{e}^{(2)} (5) \) directly determines the number of individuals with vaccine protection.
5. **Summary and discussion.** The world’s limited capacity to produce adequate vaccines over just a few months often leads to shortages of vaccines as the epidemic outbreaks. In particular for emerging pandemics, it is practical to develop fractional-dose vaccination strategies to increase population coverage in response to insufficient vaccine stockpiles. According to the trial data, authors in [35] argued that when considering pandemics and epidemics, if reduced doses are effective, it may be more beneficial to vaccinate a large portion of the population with
Figure 8. Sensitivity analyses of $\sum_{l=1}^{3} (S_{u}^{(l)}(\infty) + S_{v}^{(l)}(\infty))$ and IAR under the three optimal vaccine distribution schemes. (t1) and (u1), (t2) and (u2), and (t3) and (u3), present the effect of a change in each of $\varepsilon_{e}(2)$, $\varepsilon_{f}(2)$, $\varepsilon_{i}(2)$, $\varepsilon_{s}(2)$, and $\varepsilon_{r}(2)$ (abbreviated as e, f, i, s, and r, respectively) on the $\sum_{l=1}^{3} (S_{u}^{(l)}(\infty) + S_{v}^{(l)}(\infty))$ and IAR under the first optimal distribution scheme with $p_{1} = 1$, $p_{2} = 0.2$ and $p_{3} = 0.5$, the second optimal distribution strategy with $p_{1} = 1$, $p_{2} = 0.1$ and $p_{3} = 1$, and the third optimal distribution measure with $p_{1} = 1$, $p_{2} = p_{3} = 0.01 \times 2000/(1170 + 250)$, respectively. The size of the change is chosen by increasing and decreasing each parameter 10% off its baseline value.
reduced-dose vaccines than to vaccinate a smaller portion with full-dose vaccines. In this article, by considering the effectiveness of group-specific fractional-dose vaccination programs in heterogeneous subpopulations with proportionate mixing patterns, we proposed a multi-group SIR epidemic model that permits a distinct dose fractionation usage in each subpopulation and then systematically investigated the impact of individual-level protections (i.e., vaccine efficacy) of vaccination on the general population. The five measures of fractional-dose vaccine efficacy that we used are reduced-dose vaccine related parameters $\varepsilon_{e}(n_l)$, $\varepsilon_{f}(n_l)$, $\varepsilon_{i}(n_l)$, $\varepsilon_{s}(n_l)$ and $\varepsilon_{r}(n_l)$ with $l = 1, \ldots, K$ and $1 \leq n_l \leq 5$. On the other hand, community-level implications of different fractionated dose of candidate vaccines were described by three critical measures of the epidemic, i.e., the final size, the basic reproduction number and the infection attack rate (IAR). After developing the model, we discussed the well-posedness of the model. By virtue of the theories in Magal et al. [21], we established the existence and uniqueness of the final size of the epidemic with group-specific fractional-dose vaccination, as shown in Theorem 3.3. We also derived the the formulation of the basic reproduction number $R_0$, and further explored the relationship between the final size and $R_0$ in subsection 3.3. According to the definition of the IAR, we obtained the calculation expressions of infection attack rates for each group and the whole population.

As a case study, we also chose the epidemiology of 1957–1958 pandemic influenza A (H2N2) as the next possible pandemic strain as the authors in [18] did since the threat of reintroduction H2 subtype influenza viruses into humans remains [14, 27]. The total population is divided into three groups: child group (group 1), young adult group (group 2), and older adult group (group 3). Using numerical simulations, we first found the optimal scheme among the standard-dose only vaccination strategies with respect to the basic reproduction $R_0$, the final size related quantity $\sum_{l=1}^{3} (S_{u}^{(l)}(\infty) + S_{v}^{(l)}(\infty))$, the outbreak size, the peaking time and the IAR. Fig. 2 clearly shows that vaccinating the entire population is the best scheme but requires more vaccines when the standard-dose vaccine coverage for the target vaccination groups are the same. We also discovered that three more effective vaccine distributions in containing influenza are first group 1 then group 2 and last group 3, first group 1 then group 3 and last group 2, and first group 1 then groups 2 and 3, respectively, with the second best, which are shown in Figs. 3–4.

Then, based on the three optimal vaccine distributions obtained, we evaluated the effectiveness of 5-fold fractional-dose vaccination strategies. Under the assumption that fractional-dose vaccines will be administered to group 2 only with 5-fold fractional-dose vaccines. We considered the impacts of the five parameters $\varepsilon_{j}(5)$ with $j = e, f, i, s$, and $r$ on controlling the influenza epidemic. The simulation results presented in Figs. 5–7 show that the dose-fractionation policy is more effective in controlling the influenza epidemic than standard-dose only vaccination strategy in most cases but there exit still a few non-negligible cases (e.g., when $\varepsilon_{e}$ and $\varepsilon_{f}$ are very small) such that standard-dose only vaccination strategy is more effective than fractional-dose vaccination policy conversely, which indicate that public health authorities should cautiously propose the dose-sparing vaccination campaign to optimize the utilization of limited vaccine supplies and improve the effectiveness of such intervention programs. That is, further empirical studies for fractionated doses should be required before final dose fractionation decisions to ensure that
the fractional-dose vaccines are sufficiently effective and safe. Extra community-level benefits of lower-dose vaccination do not just require fractionated vaccines effective, but do require fractionated doses to provide high enough individual-level protections. In fact, sometimes the negative effects of lower vaccine efficacy are not offset by wider vaccine coverage, which leads to an increase in the overall IAR. Moreover, it should be noted that different administration strategies would necessarily be switched to optimize vaccination measures for certain epidemics and vaccines used in practice. These conclusions may be applicable to other vaccines fractionation cases.

At last a systematic sensitivity analysis was carried out to understand the effects of changes within the expected range of variability for each of the fractional-dose vaccines related five parameters (see Fig. 8), which highlights the need for detailed incorporation of the effects of $\varepsilon^x_2(n_2)$, $\varepsilon^y_2(n_2)$, $\varepsilon^z_2(n_2)$, and $\varepsilon^0_2(n_2)$ ($1 \leq n_2 \leq 5$) on the dynamics of the epidemic before implementing a fractional-dose vaccination strategy. Our results show that the key final size related quantity $\sum_{l=1}^{3} \left( S^{(l)}_u(\infty) + S^{(l)}_v(\infty) \right)$ is very sensitive to $\varepsilon^x_2(5)$ and $\varepsilon^y_2(5)$, and IAR is very sensitive to $\varepsilon^x_4(5)$ and $\varepsilon^z_2(5)$ for all the three optimal vaccine distribution schemes.

In our model, we used disease cases as our outcome measure, and supposed there are no latent periods in the transition from susceptible to infectious. It would be more comprehensive to address the relationship between infection and both morbidity and mortality and introduce the intrinsic birth and death rates, disease death rate, and exposed individuals into the model. These extensions of the model and their complex impacts on the fractional-dose vaccination are topics for further work.

**Acknowledgments.** We are very grateful to two anonymous referees for their careful reading and helpful suggestions which led to great improvements of our original manuscript. The authors would like to thank Dr. Yijun Lou for his valuable comments and discussion during the preparation of this paper. This work was partially funded by the Research Grants Council of Hong Kong. Zhimin Chen and Kaihui Liu would like to thank the Department of Applied Mathematics at the Hong Kong Polytechnic University for the hospitality and support during their visit. Zhimin Chen acknowledges the support of the International Training Project for Outstanding Young Scientific Research Talents in Guangdong Universities in 2018 at South China Normal University. Kaihui Liu was supported by the NNSF of China (11901247) and the Research Grants of Jiangsu University (4111190009). Xiuxiang Liu was supported in part by the NSF of Guangdong Province (2016A030313426) and the General Program of the Natural Science Foundation of Guangdong Province of China (2020A1515010445).

**Appendix A. The detailed proof of Lemma 3.2.**

**Proof.** From the $S^{(l)}_u$-equation of (1), one can obtain

\[
\frac{1}{S^{(l)}_u(t)} \cdot \frac{dS^{(l)}_u(t)}{dt} = -\sum_{m=1}^{K} \frac{c_{mn} I^{(m)}_u(t) + p_i^{(m)} \varepsilon_i^{(m)}(n_m) I^{(m)}_v(t)}{N}.
\]
Integration (9) from 0 to $t$ gives
\[
\ln S_u^{(l)}(t) - \ln S_{u0}^{(l)} = -\sum_{m=1}^{K} \frac{c_m \beta_{lm}}{N} \int_0^t I_u^{(m)}(s)\,ds
\]
\[-\sum_{m=1}^{K} \frac{c_m \beta_{lm} p_l^{(m)} \varepsilon_i^{(m)}(n_m)}{N} \int_0^t I_v^{(m)}(s)\,ds.
\] (10)

It follows from integration of the sum of the $S_u^{(l)}$-equation and the $I_u^{(l)}$-equation of (1) from 0 to $t$ that
\[
\int_0^t \left( \frac{dS_u^{(l)}(s)}{ds} + \frac{dI_u^{(l)}(s)}{ds} \right)\,ds = -\gamma_l \int_0^t I_u^{(l)}(s)\,ds.
\] (11)

By (11), we have
\[
-\int_0^t I_u^{(l)}(s)\,ds = \frac{S_u^{(l)}(t) + I_u^{(l)}(t) - S_{u0}^{(l)} - I_{u0}^{(l)}}{\gamma_l}.
\] (12)

Integrating the sum of the $S_v^{(l)}$-equation and the $I_v^{(l)}$-equation of (1) from 0 to $t$ and calculating, we obtain
\[
-\int_0^t I_v^{(l)}(s)\,ds = \frac{S_v^{(l)}(t) + I_v^{(l)}(t) - S_{v0}^{(l)} - I_{v0}^{(l)}}{\gamma_l p_r^{(l)} \varepsilon_r^{(l)}(n_t)}.
\] (13)

Substituting (12) and (13) into (10) gives
\[
\ln S_u^{(l)}(t) - \ln S_{u0}^{(l)}
= \sum_{m=1}^{K} \frac{c_m \beta_{lm}}{N \gamma_m} \left( S_u^{(m)}(t) + I_u^{(m)}(t) - S_{u0}^{(m)} - I_{u0}^{(m)} \right)
\]
\[+ \sum_{m=1}^{K} \frac{c_m \beta_{lm} p_l^{(m)} \varepsilon_i^{(m)}(n_m)}{N \gamma_m p_r^{(m)} \varepsilon_r^{(m)}(n_m)} \left( S_v^{(m)}(t) + I_v^{(m)}(t) - S_{v0}^{(m)} - I_{v0}^{(m)} \right).
\] (14)

Arranging (14) yields
\[
S_u^{(l)}(t)
= S_{u0}^{(l)} \cdot \exp \left( \sum_{m=1}^{K} \frac{c_m \beta_{lm}}{N \gamma_m} \left( S_u^{(m)}(t) - I_u^{(m)}(t) - S_{u0}^{(m)} - I_{u0}^{(m)} \right) \right)
\]
\[+ \sum_{m=1}^{K} \frac{c_m \beta_{lm} p_l^{(m)} \varepsilon_i^{(m)}(n_m)}{N \gamma_m p_r^{(m)} \varepsilon_r^{(m)}(n_m)} \left( S_v^{(m)}(t) - I_v^{(m)}(t) - S_{v0}^{(m)} - I_{v0}^{(m)} \right).
\] (15)

Then, by a calculation very similar to the derivation of (14), one admits
\[
\ln S_v^{(l)}(t) - \ln S_{v0}^{(l)}
= \sum_{m=1}^{K} \frac{c_m \beta_{lm} p_l^{(m)} \varepsilon_i^{(m)}(n_m) p_s^{(m)} \varepsilon_s^{(m)}}{N \gamma_m p_r^{(m)} \varepsilon_r^{(m)}(n_m)} \left( S_u^{(m)}(t) + I_u^{(m)}(t) - S_{u0}^{(m)} - I_{u0}^{(m)} \right)
\]
\[+ \sum_{m=1}^{K} \frac{c_m \beta_{lm} p_l^{(m)} \varepsilon_i^{(m)}(n_m) p_s^{(m)} \varepsilon_s^{(m)}}{N \gamma_m p_r^{(m)} \varepsilon_r^{(m)}(n_m)} \left( S_v^{(m)}(t) - I_v^{(m)}(t) - S_{v0}^{(m)} - I_{v0}^{(m)} \right).
\] (16)
Thus, it follows from (16) that
\[
S_v^{(l)}(t) = S_{v0}^{(l)} \cdot \exp \left( \sum_{m=1}^{K} \frac{c_m \beta_{lm} p_1^{(m)} \varepsilon_s^{(m)}(n_m)}{N \gamma_m} \left( S_u^{(m)}(t) - I_u^{(m)}(t) - S_{u0}^{(m)} - I_{u0}^{(m)} \right) \right.
\]
\[
+ \sum_{m=1}^{K} \frac{c_m \beta_{lm} p_1^{(m)} \varepsilon_s^{(m)}(n_m) p_2^{(m)} \varepsilon_r^{(m)}(n_m)}{N \gamma_m p_r^{(m)} \varepsilon_r^{(m)}(n_m)} \left( S_v^{(m)}(t) - I_v^{(m)}(t) - S_{v0}^{(m)} - I_{v0}^{(m)} \right). \tag{17}
\]

On account of \( I_u^{(m)}(\infty) = I_v^{(m)}(\infty) = 0 \) for all \( 1 \leq m \leq K \), we get (4) and (5) by letting \( t \) tends to infinity on both sides of (15) and (17). The proof of Lemma 3.2 is complete.

\[\square\]

REFERENCES

[1] V. Andreasen, The final size of an epidemic and its relation to the basic reproduction number, Bull. Math. Biol., 73 (2011), 2305–2321.
[2] A. C. Campi-Azevedo, P. de Almeida Estevam, J. G. Coelho-Dos-Reis and et al., Subdoses of 17DD yellow fever vaccine elicit equivalent virological/immunological kinetics timeline, BMC Infect. Dis., 14 (2014), 1–12.
[3] Z. Chen, K. Liu, X. Liu and Y. Lou, Modelling epidemic with fractional-dose vaccination in response to limited vaccine supply, J. Theor. Biol., 468 (2020), 110865, 10pp.
[4] L. Chow, M. Fan and Z. Feng, Dynamics of a multigroup epidemiological model with group-targeted vaccination strategies, J. Theor. Biol., 291 (2011), 56–64.
[5] J. Cui, Y. Zhang and Z. Feng, Influence of non-homogeneous mixing on final epidemic size in a meta-population model, J. Biol. Dyn., 13 (2019), 31–46.
[6] D. Ding and X. Ding, Global stability of multi-group vaccination epidemic models with delays, Nonlinear Anal. Real World Appl., 12 (2011), 1991–1997.
[7] S. Gandon, M. J. Mackinnon, S. Nee and A. F. Read, Imperfect vaccines and the evolution of pathogen virulence, Nature, 414 (2001), 751–755.
[8] P. Guerin, L. Næss, C. Fogg and et al., Immunogenicity of fractional doses of tetravalent A/C/Y/W135 meningococcal polysaccharide vaccine: Results from a randomized non-inferiority controlled trial in uganda, PLoS Negl. Trop. Dis., 2 (2008), e342.
[9] P. Haldar, P. Agrawal, P. Bhatnagar and et al., Fractional-dose inactivated poliovirus vaccine, India, Bull. World Health Organ., 97 (2019), 328–334.
[10] J. K. Hale, Ordinary Differential Equations, New York: Robert E. Krieger Publishing Company, Inc., Huntington, 1980.
[11] M. E. Halloran, C. J. Struchiner and I. M. Longini Jr, Study designs for evaluating different efficacy and effectiveness aspects of vaccines, Am. J. Epidemiol., 146 (1997), 789–803.
[12] I. F. Hung, Y. Levin, K. K. To and et al., Dose sparing intradermal trivalent influenza (2010/2011) vaccination overcomes reduced immunogenicity of the 2009 H1N1 strain, Vaccine, 30 (2012), 6427–6435.
[13] E. Jonkera, M. van Ravenhorst, G. Berbers and L. Visser, Safety and immunogenicity of fractional dose intradermal injection of two quadrivalent conjugated meningococcal vaccines, Vaccine, 36 (2018), 3727–3732.
[14] U. Joseph, M. Linster, Y. Suzuki and et al., Adaptation of pandemic H2N2 influenza a viruses in humans, J. Virol., 89 (2015), 2442–2447.
[15] W. O. Kermack and A. G. McKendrick, A contribution to the mathematical theory of epidemics, Proc. Math. Phys. Eng. Sci., 15 (1927), 700–721.
[16] V. Künni, J. M. Klap, M. K. Seiberling and et al., Immunogenicity and safety of low dose virosomal adjuvanted influenza vaccine administered intradermally compared to intramuscular full dose administration, Vaccine, 27 (2009), 3561–3567.
[17] S. Lee, R. Morales and C. Castillo-Chavez, A note on the use of influenza vaccination strategies when supply is limited, Math. Biosci. Eng., 8 (2011), 171–182.
[18] I. M. Longini, M. E. Halloran, A. Nizam and Y. Yang, Containing pandemic influenza with antiviral agents, *Am. J. Epidemiol.*, **159** (2004), 623–633.

[19] J. Ma and D. J. D. Earn, Generality of the final size formula for an epidemic of a newly invading infectious disease, *Bull. Math. Biol.*, **68** (2006), 679–702.

[20] P. Magal, O. Seydi and G. Webb, Final size of an epidemic for a two-group SIR model, *SIAM J. Appl. Math.*, **76** (2016), 2042–2059.

[21] P. Magal, O. Seydi and G. Webb, Final size of a multi-group SIR epidemic model: Irreducible and non-irreducible modes of transmission, *Math. Biosci.*, **301** (2018), 59–67.

[22] R. M. Martins, M. D. Maia, R. H. Farias, L. A. Camacho, M. S. Freire, R. Galler and et al., 7dd yellow fever vaccine: A double blind, randomized clinical trial of immunogenicity and safety on a dose-response study, *Hum. Vaccin. Immunother.*, **9** (2013), 879–888.

[23] A. J. Mohammed, S. Alawaidy, S. Bawikar and et al., Fractional doses of inactivated poliovirus vaccine in Oman, *N. Engl. J. Med.*, **362** (2010), 2351–2359.

[24] J. Mossong, N. Hens, M. Jit and et al., Social contacts and mixing patterns relevant to the spread of infectious diseases, *PLoS Med.*, **5** (2008), e74.

[25] W. Qin, S. Tang and R. A. Cheke, Nonlinear pulse vaccination in an SIR epidemic model with resource limitation, *Abstr. Appl. Anal.*, **2013** (2013), 1–13.

[26] L. Rass and J. Radcliffe, *Spatial Deterministic Epidemics*, Rhode Island: Mathematical Surveys and Monographs, 2003.

[27] Z. B. Reneer and T. M. Ross, H2 influenza viruses: Designing vaccines against future H2 pandemics, *Biochem. Soc. Trans.*, **47** (2019), 251–264.

[28] S. Resik, A. Tejeda, R. W. Sutter and et al., Priming after a fractional dose of inactivated poliovirus vaccine, *N. Engl. J. Med.*, **368** (2013), 416–424.

[29] S. Riley, J. T. Wu and G. M. Leung, Optimizing the dose of pre-pandemic influenza vaccines to reduce the infection attack rate, *PLoS Med.*, **4** (2007), e218.

[30] A. H. Roukens, K. van Halem, A. W. de Visser and L. G. Visser, Long-term protection after fractional-dose yellow fever vaccination: Follow-up study of a randomized, controlled, noninferiority trial, *Ann. Intern. Med.*, **169** (2018), 1761–1765.

[31] A. H. Roukens, A. C. Vossen, P. J. Breedenbeek, J. T. van Dissel and L. G. Visser, Intradermally administered yellow fever vaccine at reduced dose induces a protective immune response: A randomized controlled non-inferiority trial, *PLoS One*, **3** (2008), e1993.

[32] H. L. Smith and P. Waltman, *The Theory of the Chemostat: Dynamics of Microbial Competition*, New York: Cambridge University Press, 1995.

[33] P. van den Driessche and J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Math. Biosci.*, **180** (2002), 29–48.

[34] J. T. Wu, C. M. Peak, G. M. Leung and M. Lipsitch, Fractional dosing of yellow fever vaccine of extend supply: A modelling study, *Lancet*, **388** (2016), 2904–2911.

[35] K. N. Wyatt, G. J. Ryan and K. A. Sheerin, Reduced-dose influenza vaccine, *Ann. Pharmacother.*, **40** (2006), 1635–1639.

[36] T. Yu, D. Cao and S. Liu, Epidemic model with group mixing: Stability and optimal control based on limited vaccination resources, *Commun. Nonlinear Sci. Numer. Simul.*, **61** (2018), 54–70.

Received September 2020; revised January 2021.

E-mail address: chenzm@m.scnu.edu.cn
E-mail address: katrina.liu@connect.polyu.hk
E-mail address: liuxiuxiang@m.scnu.edu.cn