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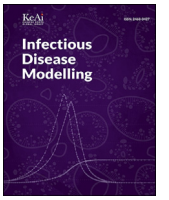

Understanding the impact of disease and vaccine mechanisms on the importance of optimal vaccine allocation

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ABSTRACT

Vaccination is an important epidemic intervention strategy. However, it is generally unclear how the outcomes of different vaccine strategies change depending on population characteristics, vaccine mechanisms and allocation objective. In this paper we develop a conceptual mathematical model to simulate strategies for pre-epidemic vaccination. We extend the SEIR model to incorporate a range of vaccine mechanisms and disease characteristics. We then compare the outcomes of optimal and suboptimal vaccination strategies for three public health objectives (total infections, total symptomatic infections and total deaths) using numerical optimisation. Our comparison shows that the difference in outcomes between vaccinating optimally and suboptimally depends on vaccine mechanisms, disease characteristics, and objective considered. Our modelling finds vaccines that impact transmission produce better outcomes as transmission is reduced for all strategies. For vaccines that impact the likelihood of symptomatic disease or dying due to infection, the improvement in outcome as we decrease these variables is dependent on the strategy implemented. Through a principled model-based process, this work highlights the importance of designing effective vaccine allocation strategies. We conclude that efficient allocation of resources can be just as crucial to the success of a vaccination strategy as the vaccine effectiveness and/or amount of vaccines available.

1. Introduction

Pre-epidemic vaccination is an important intervention for managing disease, and when supply is limited vaccines should be used strategically as part of pandemic preparedness. The difference in the outcomes of various allocation strategies will depend on the characteristics of the pathogen and on vaccine mechanisms. Understanding how these characteristics affect both the

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optimal allocation strategy and the difference in outcomes between strategies is vital when planning vaccine allocation for novel pathogens or pathogen strains.

When new viruses emerge, decision-makers aim to design effective vaccination strategies based on knowledge of previous pandemics and emerging information (Australian Government Department of Health, 2019; Coburn, Wagner, & Blower, 2009). For example, when vaccinating against influenza, there are benefits to targeting vaccination towards those most vulnerable to disease, and targeting vaccination towards those most likely to spread disease (Degeling et al., 2021; Dushoff et al., 2007). However, these benefits are highly dependent on disease parameters as well as relative efficacy of the vaccine between population groups (Keeling & Rohani, 2008; Keeling & White, 2011). When vaccines are available or potential vaccines are in development for novel pathogens, modelling has been used to develop optimal vaccination strategies (Foy et al., 2021; Shim, 2021). However, any strategy developed must be regularly reevaluated as knowledge of pathogen and vaccine characteristics improves and/or new virus variants emerge. For example, the emergence of new variants for COVID-19 in 2021, notably the Delta and Omicron variants, has necessitated the reevaluation of current intervention strategies. As we have learnt more about the Delta and Omicron variants, many countries have adapted their vaccination strategies to prioritise booster doses (Dolgin, 2021; Kenyon, 2021), partly due to decreased vaccine effectiveness against new variants.

Mathematical modelling provides the tools to quantify how vaccine mechanisms and disease characteristics impact the outcomes of vaccine allocation. For simple epidemiological models such as the SIR or SEIR model, we can calculate the threshold vaccination needed to ensure $R_0 < 1$ which ensures sustained transmission is not possible. While we can derive the threshold of vaccination to ensure $R_0 < 1$ for more complex models, the relationship between various objectives such as total infections or deaths and R_0 is no longer as simple as before. As such, calculating the number of vaccines needed to optimise a specific objective requires careful thought and potentially numerical methods. In practice, we could instead simulate a range of strategies to determine which results in the best outcome for our objective (Dushoff et al., 2007; Foy et al., 2021; Lee, Golinski, & Chowell, 2012; Shim, 2021). The choice of public health objective will often impact results, so we need to consider which metrics, such as total infections, total symptomatic infections or total deaths, are most appropriate to minimise when optimising a vaccine allocation strategy (Probert et al., 2016).

When a new epidemic threatens to establish, decision makers often prepare vaccination strategies based on either known disease characteristics, or emerging knowledge of a novel disease. For influenza and COVID-19, vaccines are generally most effective when allocated early in the outbreak and rapidly, focusing primarily on vulnerable people and highly transmissible groups (Degeling et al., 2021; Dushoff et al., 2007; Keeling & White, 2011; Medlock & Galvani, 2009; Teo, Bean, & Ross, 2021). However, optimal vaccine strategies depend on how transmissibility, severity and vaccine effectiveness vary by age (Degeling et al., 2021; Foy et al., 2021; Lee et al., 2012; Matrajt et al., 2021a; Moore, Hill, Dyson, Tildesley, & Keeling, 2021; Shim, 2021). While these analyses focus on determining the optimal vaccine allocation strategy given pathogen characteristics, they do not present a generalised understanding of difference between optimal and suboptimal strategies. Are there certain situations where vaccine coverage should be prioritised, irrespective of who gets vaccinated? Or will we only see an improved outcome from increasing vaccine coverage if we allocate well?

In this paper we develop a model to simulate the outcomes of different vaccination strategies under a variety of disease characteristics, vaccine mechanisms and allocation objectives. We develop a deterministic model incorporating four separate vaccine mechanisms and a population comprised of two sub-groups with varying characteristics. Vaccination is assumed to occur prior to the establishment of the epidemic in our population. This scenario could correspond to vaccinating before a disease is introduced or during a time of low community transmission. We then determine the optimal allocation strategies for this population for three allocation objectives: total infections, symptomatic infections or deaths. Through comparing the outcomes of optimal and suboptimal allocation strategies, we investigate how disease characteristics (such as R_0 and the probability of dying due to infection) and vaccine characteristics (such as vaccine effectiveness and coverage) impact the differences in outcomes for various strategies. This analysis explores how the difference in outcomes from prioritising better vaccine resources or prioritising targeted allocation changes depending on the scenario considered.

2. Method

We define a modified SEIR model which includes two population groups, pre-epidemic vaccination, symptomatic and asymptomatic infection, and death due to disease. We consider vaccine mechanisms that reduce transmission, the probability of symptomatic infection or the probability of death due to infection, and consider scenarios where people are vaccinated before an epidemic starts. Through numerical simulation of our model, we aim to minimise either total infections, symptomatic infections or deaths and explore how disease and vaccine characteristics affect the outcome of three allocation objectives.

2.1. Model assumptions and definition

We define our model from the following disease progression for each population group:

- Every person is initially susceptible and is designated *unvaccinated* or *vaccinated* based on their pre-epidemic vaccination status.
- If infected, a susceptible person becomes *exposed*, where they are infected but not yet infectious.

- An exposed person will become infectious, developing either *symptomatic* or *asymptomatic disease.*
- A person with symptomatic disease can either *recover* from disease, or *die* due to infection.
- A person with asymptomatic disease will *recover* from disease.

Our model is described by the compartment diagram in Fig. 1. We consider compartments X_{jki}, where:

- $X \in \{U, V, E, I, R, D\}$: denotes compartment types; *Unvaccinated, Vaccinated, Exposed, Infected, Recovered* and *Dead.*
- $j \in \{U, V\}$: denotes *Unvaccinated* or *Vaccinated* people,
- $k \in \{S, A\}$: denotes *Symptomatic* or *Asymptomatic* infection, and
- $i \in \{1, 2\}$: denotes subpopulation group, denoted Group 1 and Group 2.

For example, the compartment I_{US1} is comprised of people in Group 1 who were initially unvaccinated and have developed symptomatic infection.

To illustrate the impact of vaccination on subpopulation groups with varying characteristics, we define Group 1 as twice as susceptible to infection as Group 2. We define the contact matrix C to characterise the interactions between susceptible and infectious individuals in each group:

$$C = \begin{array}{c} \\ \mathbb{S}_1 \\ \mathbb{S}_2 \end{array} \begin{array}{c} \begin{array}{cc} \mathbb{I}_1 & \mathbb{I}_2 \end{array} \\ \begin{bmatrix} 2 & 2 \\ 1 & 1 \end{bmatrix} \end{array}, \tag{1}$$

where $\mathbb{S} = \{U_i, V_i\}$ denotes the susceptible compartments and $\mathbb{I} = \{I_{USi}, I_{UAi}, I_{VSi}$ and $I_{VAi}\}$ denotes the infected compartments. That is, we can define the force of infection $\lambda_i(t)$ for each subpopulation group i by:

$$\lambda_i(t) = \sum_{j=1}^{2} \sum_{K \in \mathbb{I}} a_{K_j} \beta C_{ij} \frac{K_j(t)}{LP_j(t)} \tag{2}$$

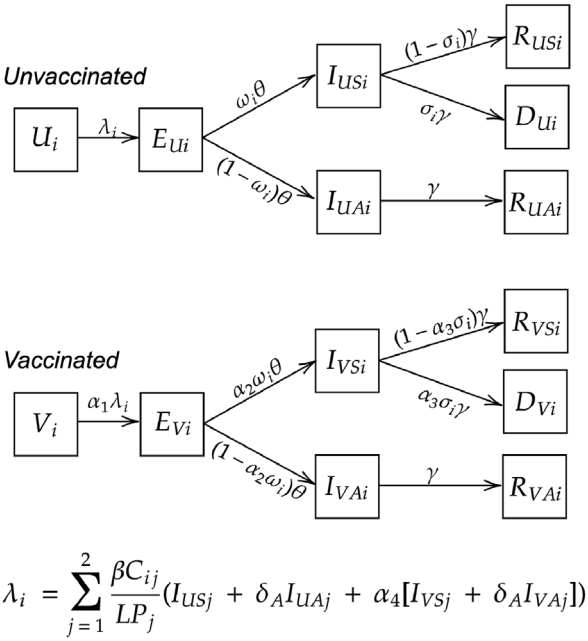


Fig. 1. Compartmental diagram for our extended SEIR model. Initially people are either susceptible (U_i) or vaccinated (V_i) where $i \in \{1, 2\}$ denotes population group. Both classes are able to become exposed (E_{ji}) at rate and then infected (I_{jki}) where $j \in \{U, V\}$ denotes whether they were initially unvaccinated or vaccinated and $k \in \{S, A\}$ denotes if they experience symptomatic or asymptomatic disease. From here, symptomatic and asymptomatic people can recover from disease (R_{jki}) or symptomatic people can also die due to disease (D_{ji}). As defined in the standard SEIR model, θ denotes the rate at which people transition from exposed to infected and γ denotes the rate at which people are removed from infected compartments. In this model, ω_i denotes the probability of developing symptomatic infection and σ_i denotes the probabiity of dying due to disease. We define vaccine effectiveness for each mechanism as $1 - \alpha_m$ for $m \in \{1, 2, 3, 4\}$. We consider mechanisms: 1) reducing susceptibility, 2) reducing probability of developing symptomatic infection, 3) reducing probability of dying due to disease, and 4) reducing infectivity. In the force of infection λ_i, βC_{ij} denotes the transmission rate between a susceptible in Group i and an infected in Group j. $1 - \delta_A$ denotes the reduction in infectivity due to asymptomatic infection and LP_j denotes the number of people alive in Group j.

where β is the transmission rate, a_{Kj} scales β to suit the characteristics of compartment K_j, and $LP_j(t)$ is the number of people alive in Group j at time t.

We choose to vary our transmission parameter β through varying the reproductive number, R_0. We calculate R_0 numerically for our model by finding the largest eigenvalue of the next generation matrix (Diekmann, Heesterbeek, & Roberts, 2010). Using this calculation, we calibrate β for a given R_0 value.

In this model, we assume frequency dependent transmission i.e. the transmission rate depends on the proportion of infecteds in the population as the contact rate is independent of population size. This is preferred for modelling human populations over density dependent transmission as we determine our contacts by social constraints, which do not necessarily scale with population size (Keeling & Rohani, 2008). We further assume the epidemic progresses on a fast enough timescale that we can ignore births and natural deaths, and that the population is closed. Therefore, the total population of each group $P_{i\in\{1,2\}}$ is constant, but this population also includes people who have died due to disease. To implement frequency dependent transmission, we define a new population size $LP_{i\in\{1,2\}}(t)$ which denotes the size of the *living* population for each group. This living population will change over time as people die due to disease. In our model, dead people no longer have contact with living people, so for the same number of infected people, the proportion of infected contacts will increase.

To investigate the effects of a range of vaccine mechanisms, we consider four vaccine mechanisms (Moore et al., 2021):

1. Reduction in susceptibility,
2. Reduction in probability of developing symptomatic infection,
3. Reduction in probability of dying due to disease, and
4. Reduction in infectivity.

We define the effectiveness of each vaccine as $1 - \alpha_{m\in\{1,2,3,4\}} \in [0, 1]$, where m denotes the vaccine mechanism, as numbered above. A 100% effective vaccine ($1 - \alpha_m = 1$) corresponds to a perfect vaccine. Conversely, a 0% effective vaccine ($1 - \alpha_m = 0$) corresponds to the vaccine having no effect. When vaccine effectiveness is not varied, we use a baseline value of $1 - \alpha_m = 0.75$. As we only consider pre-epidemic vaccination, vaccine allocation appears in the initial conditions for the vaccinated compartments for Groups 1 and 2 (V_1 and V_2). We assume those with asymptomatic infection are less infectious than those with symptomatic infection (this reduction in infectivity is given by the quantity $1 - \delta_A = 0.5$).

From the assumptions stated above, we derive the ODEs to describe our model. In addition to the standard SEIR model parameters, $1 - \alpha_m$ denotes the vaccine effectiveness, ω_i denotes the proportion of exposed individuals that become symptomatically infected, σ_i denotes the proportion of symptomatic individuals who die due to disease, and $1 - \delta_A$ denotes the reduction in infectivity for asymptomatic infecteds, all for a population group i. Furthermore, λ_i denotes the force of infection, as defined by Eq. (2), C_{ij} denotes the elements of the contact matrix, as defined by Eq. (1), P_j denotes the size of Group j at the beginning of the epidemic, and $LP_j(t)$ denotes the size of the living population of Group j. Therefore, our model for each population group i is:

2.1.1. Unvaccinated

$$\frac{dU_i}{dt} = -\lambda_i(t)U_i(t) \tag{3}$$

$$\frac{dE_{Ui}}{dt} = \lambda_i(t)U_i(t) - \theta E_{Ui}(t) \tag{4}$$

$$\frac{dI_{USi}}{dt} = \omega_i\theta E_{Ui}(t) - \gamma I_{USi}(t) \tag{5}$$

$$\frac{dI_{UAi}}{dt} = (1-\omega_i)\theta E_{Ui}(t) - \gamma I_{UAi}(t) \tag{6}$$

$$\frac{dR_{USi}}{dt} = (1-\sigma_i)\gamma I_{USi}(t) \tag{7}$$

$$\frac{dD_{Ui}}{dt} = \sigma_i\gamma I_{USi}(t) \tag{8}$$

$$\frac{dR_{UAi}}{dt} = \gamma I_{UAi}(t) \tag{9}$$

2.1.2. Vaccinated

$$\frac{dV_i}{dt} = -\alpha_1 \lambda_i(t) V_i(t) \tag{10}$$

$$\frac{dE_{Vi}}{dt} = \alpha_1 \lambda_i(t) V_i(t) - \theta E_{Vi}(t) \tag{11}$$

$$\frac{dI_{V\,Si}}{dt} = \alpha_2 \omega_i \theta E_{Vi}(t) - \gamma I_{V\,Si}(t) \tag{12}$$

$$\frac{dI_{V\,Ai}}{dt} = (1-\alpha_2 \omega_i)\theta E_{Vi}(t) - \gamma I_{V\,Ai}(t) \tag{13}$$

$$\frac{dR_{V\,Si}}{dt} = (1-\alpha_3 \sigma_i)\gamma I_{V\,Si}(t) \tag{14}$$

$$\frac{dD_{Vi}}{dt} = \alpha_3 \sigma_i \gamma I_{V\,Si}(t) \tag{15}$$

$$\frac{dR_{V\,Ai}}{dt} = \gamma I_{V\,Ai}(t). \tag{16}$$

2.1.3. Force of infection

$$\lambda_i(t) = \sum_{j=1}^{2} \beta C_{ij} \frac{I_{USj}(t)}{LP_j(t)} + \delta_A \beta C_{ij} \frac{I_{UAj}(t)}{LP_j(t)} + \alpha_4 \left[\beta C_{ij} \frac{I_{V\,Sj}(t)}{LP_j(t)} + \delta_A \beta C_{ij} \frac{I_{V\,Aj}(t)}{LP_j(t)} \right] \tag{17}$$

$$\Rightarrow \lambda_i(t) = \sum_{j=1}^{2} \frac{\beta C_{ij}}{LP_j(t)} \left(I_{USj}(t) + \delta_A I_{UAj}(t) + \alpha_4 \left[I_{V\,Sj}(t) + \delta_A I_{V\,Aj}(t) \right] \right) \tag{18}$$

Adding Eqs. 3–16 we find:

$$\sum_{\substack{i\in\{1,2\} \\ j\in\{U,V\} \\ k\in\{S,A\}}} \frac{dU_i}{dt} + \frac{dV_i}{dt} + \frac{dE_{ji}}{dt} + \frac{dI_{jki}}{dt} + \frac{dR_{jki}}{dt} + \frac{dD_{ji}}{dt} = 0$$

$$\Rightarrow \sum_{\substack{i\in\{1,2\} \\ j\in\{U,V\} \\ k\in\{S,A\}}} U_i(t) + V_i(t) + E_{ji}(t) + I_{jki}(t) + R_{jki}(t) + D_{ji}(t) = \sum_{i\in\{1,2\}} P_i,$$

where we define P_1 and P_2 as the population sizes of Groups 1 and 2 at the beginning of the epidemic. For our analysis we assume P_1=P_2. As the epidemic progresses and people die due to disease, we define the living population size $LP_{i\in\{1,2\}}(t)$ as:

$$LP_i(t) = P_i - D_{Ui}(t) - D_{Vi}(t).$$

Given both Groups 1 and 2 start with I_0 total infections each, and v_1 and v_2 vaccinations respectively, Eqns 3–16 have the following initial conditions:

$$
\begin{aligned}
U_i(0) &= P_i - v_i - I_0 \\
V_i(0) &= v_i \\
E_{ji}(0) &= 0 \\
I_{Uki}(0) &= \frac{1}{2} I_0 \\
I_{V\,ki}(0) &= 0 \\
R_{jki}(0) &= 0 \\
D_{ji}(0) &= 0,
\end{aligned}
$$

for $i \in \{1, 2\}$, $j \in \{U, V\}$ and $k \in \{S, A\}$. That is, we assume there are initially $2I_0$ infected people with I_0 infected people in each population group. For each population group all initially infected people are unvaccinated with half symptomatic and the other half asymptomatic. In our analysis we assume $I_0 = 50$, that is there are 100 people initially infected across the whole population. Complete modelling details and baseline parameters are given in Section S1 of the supplementary material.

2.2. Optimising vaccine allocation

To find the optimal vaccine allocation strategy, we compute the number of vaccines allocated to each subpopulation group to minimise a given objective function. Given we consider a finite number of vaccines ($v_{\max}$) and two subpopulation groups, the problem reduces to finding the number of vaccines allocated to Group 1 (v_{opt}) that minimise the objective function:

$$v_{opt} = \min_{v \in \{1,\ldots,v_{max}\}} \{\text{objective function}(y(v))\}, \tag{19}$$

where y is the output from the model Eqs. 3–16 with initial conditions $V_1(0) = v$ and $V_2(0) = v_{\max} - v$.

We consider three objective functions:

1. Total infections:

$$\sum_{i \in \{1,2\}} \sum_{j \in \{U,V\}} \sum_{k \in \{S,A\}} R_{jki}(t_{\text{end}}) + D_{ji}(t_{\text{end}})$$

2. Total symptomatic infections:

$$\sum_{i \in \{1,2\}} \sum_{j \in \{U,V\}} R_{jSi}(t_{\text{end}}) + D_{ji}(t_{\text{end}})$$

3. Total deaths:

$$\sum_{i \in \{1,2\}} \sum_{j \in \{U,V\}} D_{ji}(t_{\text{end}})$$

where $X(t_{\text{end}})$ denotes the size of compartment X at the end of the epidemic. In our model, to calculate our objective functions we assume $t_{end} = 200$ days as for each combination of parameters considered, the epidemic had died out by this time.

We aim to compare optimal and suboptimal strategies as we vary disease and vaccine characteristics. To calculate the optimal strategy for any set of parameter values, we use the MATLAB function fmincon to find the proportion of vaccines allocated to each group that minimises the objective (total infections, total symptomatic infections, or total deaths). We started our optimisation algorithm from three different allocations and we either found one optimal strategy, or all strategies were optimal (i.e. vaccination had no impact on our objective).

For our model and parameters considered, when we found one optimal strategy, it prioritised vaccinating one group over another. Using this optimal strategy, we compute sub-optimal strategies by varying the proportion of vaccines allocating to each group. In particular, we define a "poor strategy" as prioritising vaccination for the opposite group to the optimal strategy. We also define an "uninformed strategy" as vaccinating each group equally.

The results presented were generated using MATLAB 9.10, and our model was simulated using ode45.

3. Results

We present our results to investigate the following questions:

1. How do disease characteristics lead to variation in the differences in outcomes between optimal and suboptimal vaccination strategies?
2. How does the difference in outcome between optimal and suboptimal strategies depend on vaccine effectiveness and coverage?

To discuss our results, we consider how the modelled disease characteristics and vaccine mechanisms impact an objective. In the context of our modelling, we define this impact as:

- *Direct:* the disease characteristic/vaccine mechanism impacts the allocation objective for only vaccinated people; and/or
- *Indirect:* the disease characteristic/vaccine mechanism impacts the allocation objective for both vaccinated and unvaccinated people.

For example, in our model vaccine mechanisms 1 and 4 reduce transmission which reduces infections, symptomatic infections and deaths for both vaccinated and unvaccinated people. We consider these mechanisms to *indirectly* impact total infections, symptomatic infections and deaths. On the other hand, vaccine mechanism 3 reduces the likelihood of dying due to infection which reduces deaths for vaccinated people, but as modelled does not impact transmission. We consider this mechanism to *directly* impact total deaths.

The figures in Section 3.1: varying disease characteristics and Section 3.2: varying vaccine characteristics compare vaccination strategies as we vary parameters. We use solid and dotted lines to represent how the (1) optimal, (2) poor and (3) uninformed strategies perform as we vary our considered parameters.

In the following sections we provide a subset of modelling results, deliberately chosen to explore interesting aspects of our modelling. However, we also provide the complete set of model results in the supplementary material. The figures in Section 2 of the supplementary material show how the outcomes of various vaccine strategies differ for all combinations of vaccine mechanism, allocation objective and considered parameter values.

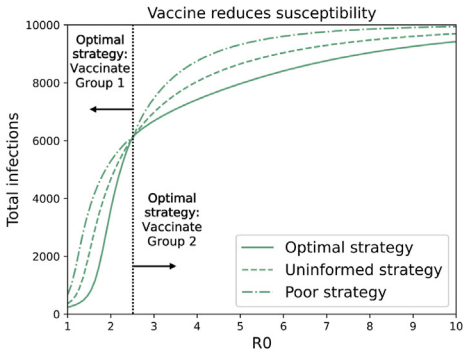
3.1. Varying disease characteristics

Here we explore the difference between optimal and suboptimal strategies when varying disease characteristics. We consider vaccination strategies for a 75% effective vaccine with 50% vaccine coverage. These values have been chosen deliberately to demonstrate the effects of varying disease characteristics and are broadly reasonable in terms of typical vaccine effectiveness measures for respiratory diseases (Coelingh, Olajide, MacDonald, & Yogev, 2015; McVernon et al., 2021; Wilkinson et al., 2017). As we assume Group 1 and Group 2 are the same size, 50% vaccine coverage provides interesting results as it gives us the potential to vaccinate the entirety of one population group. Unless otherwise stated, we assume a total population of size of $N = 10000$, with 5000 people in each group ($P_1 = P_2 = 5000$).

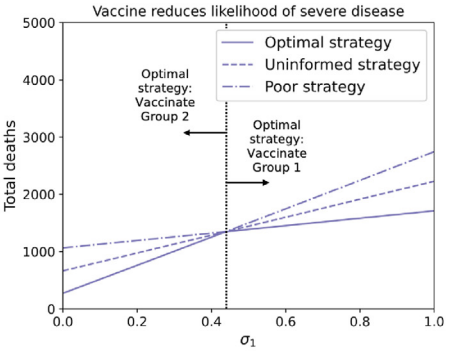
The plots in Fig. 2 show how varying a transmission parameter (reproduction number: R_0) and another that indicates infection characteristics (probability of dying due to infection for Group 1: σ_1) affects the difference between optimal and suboptimal allocation strategies. Note that Fig. 2a and b consider different vaccine mechanisms and allocation objectives.

(a) Total **infections** for a vaccine that reduces susceptibility by 75% with 50% coverage for three allocation strategies as we continuously vary R_0.
(b) Total **deaths** for a vaccine that reduces the probability of dying due to infection by 75% with 50% coverage for three allocation strategies as we vary the probability of dying due to infection for Group 1 (σ_1). The probability of dying due to infection for Group 2 is constant, $\sigma_2 = 0.5$. Note the reduced scale for total deaths.

We consider two regions in Fig. 2a defined by the value $R_0' \approx 2.5$ for which the optimal strategy changes: low R_0 ($R_0 < R_0'$) and high R_0 ($R_0 > R_0'$). For low R_0, there are few secondary infections (due to vaccination), and so the total infections is dominated by the number of initially infected people (I_0). In our model there are 100 people intially infected, and so the curves in Fig. 2a are initially convex, which is not seen in typical final size curves due to the assumption of very small I_0 ($I_0 \approx 1\%$ of the total population). For high R_0 we recover the typical final size curve.



(a) Total **infections** for a vaccine that reduces susceptibility by 75% with 50% coverage for three allocation strategies as we continuously vary R_0.



(b) Total **deaths** for a vaccine that reduces the probability of dying due to infection by 75% with 50% coverage for three allocation strategies as we vary the probability of dying due to infection for Group 1 (σ_1). The probability of dying due to infection for Group 2 is constant, $\sigma_2 = 0.5$. Note the reduced scale for total deaths.

Fig. 2. Comparing the differences between strategies for varying vaccine mechanisms and allocation objectives as we vary R_0 and the probability of dying due to infection for Group 1 σ_1. Note the different vaccine mechanisms and allocation objectives for each figure.

Qualitatively, we see a difference in total infections for *all strategies* as we vary R_0. While the difference in total infections for high and low R_0 depends on the strategy we choose, for all strategies total infections monotonically increase with R_0. At $R_0 = R_0'$, the total infections from the optimal, uninformed and poor strategies overlap as the optimal strategy changes from prioritising vaccination for Group 1 to prioritising vaccination for Group 2. As R_0 approaches the critical value of R_0', more people in Group 1 will be infected despite vaccination, closing the gap between the total infections from optimal and sub-optimal strategies (more details can be found in Section S2.1 of the supplementary material). As R_0 increases above 5, the total infections for all strategies gets consistently worse and the difference between strategies decreases.

In contrast, we consider the effect of varying the likelihood of dying due to infection for Group 1 (σ_1) on the difference in total deaths between strategies, shown in Fig. 2b. The likelihood of dying due to infection for Group 2 is held constant at $\sigma_2 = 0.5$. We consider three scenarios: Group 1 has higher risk of dying due to infection than Group 2 ($\sigma_1 > \sigma_2$), Group 2 has higher risk than Group 1 ($\sigma_2 > \sigma_1$), and both groups have approximately equal risk ($\sigma_1 \approx \sigma_2$). When $\sigma_1 \approx \sigma_2$, the only factor influencing the difference in deaths between population groups is their relative susceptibility (as defined previously). In Fig. 2b, when $\sigma_1 \approx \sigma_2$ there is a difference in the number of people infected in each population group, but vaccination will reduce the likelihood of dying due to disease similarly for both groups. In this scenario there is limited benefit in vaccinating one group over another. However, when $\sigma_1 \not\approx \sigma_2$, one group is more likely to die due to infection than another. As both the vaccine mechanism and disease characteristic considered *directly* impact the allocation objective (total deaths), the difference in outcome between allocation strategies is dependent on the difference between σ_1 and σ_2. As one group becomes much more likely to die due to infection than the other, we see a widening gap between the total deaths from the optimal and poor strategies, with the optimal strategy being to vaccinate those most at risk.

The two examples presented in Fig. 2 demonstrate how direct and indirect effects of vaccination impact the differences in outcomes (total infections or total deaths) between optimal and suboptimal strategies. For parameters indirectly impacting the allocation objective (e.g. R_0) the difference between outcomes of strategies is dependent on the value of the parameter itself. This is also demonstrated in Figs. S2a, S5, S10, S11, S13, S14 and S17 in the supplementary which show the difference between outcomes as we vary ω_1, δ_A, and R_0 for different vaccine mechanisms. However, for parameters directly impacting the allocation objective (e.g. σ_1) the difference between outcomes of strategies is dependent on the relative parameter values between each population group. The biggest differences between outcomes of strategies will occur where there is large disparity in the parameter between groups, and the smallest difference when the parameters for both groups are approximately equal. This is also demonstrated in Figs. S2b, S2c, S3, S4c, S6c and S7c in the supplementary which show the difference between outcomes as we vary ω_1 and σ_1 for different vaccine mechanisms.

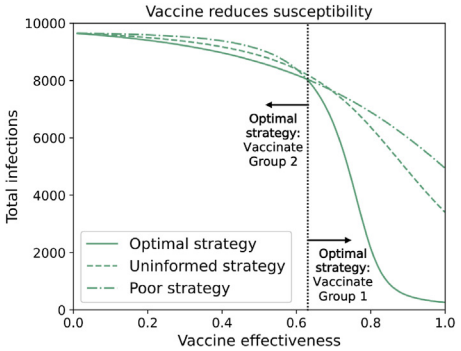
3.2. Varying vaccine effectiveness and coverage

We now consider an example population to demonstrate how vaccine effectiveness and coverage impact the differences in outcomes between allocation strategies. We define Group 1 to be more susceptible, more likely to develop symptomatic disease and more likely to die due to disease, and Group 2 to be less susceptible, less likely to develop symptomatic disease and less likely to die due to disease.

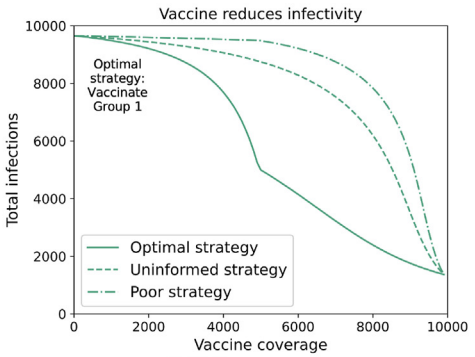
(a) Total **infections** for a vaccine that reduces susceptibility for three allocation strategies as we vary vaccine effectiveness.
(b) Total **infections** for a vaccine that reduces infectivity for three allocation strategies as we vary vaccine coverage.
(c) Total **symptomatic infections** for a vaccine that reduces the probability of developing symptomatic infection for three allocation strategies as we vary vaccine effectiveness.
(d) Total **deaths** for a vaccine that reduces the probability of dying due to infection for three allocation strategies as we vary vaccine coverage. Note the reduced scale for total deaths.

Fig. 3 compares the differences between allocation strategies for various vaccine mechanisms and allocation objectives as we vary vaccine effectiveness and coverage. Fig. 3a and b shows the total infections for vaccines that impact transmission as vaccine effectiveness and coverage are varied. Both figures demonstrate vaccine mechanisms that indirectly impact the allocation objective. As we saw for R_0 in Fig. 2a, increasing vaccine effectiveness or coverage results in fewer total infections for *all* strategies. This demonstrates that, under the assumptions of our model, securing more vaccines or more effective vaccines will work to decrease our objective, even under a suboptimal strategy. This is also demonstrated in Figs. S18, S21, S22, S25 in the supplementary which show the difference between outcomes for vaccines that reduce susceptibility or infectivity as we vary vaccine effectiveness and coverage.

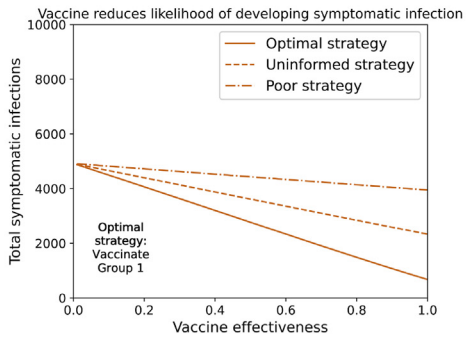
Fig. 3c and d shows how total symptomatic infections and total deaths for vaccines that impact individual infection vary as we change vaccine effectiveness and coverage. In Fig. 3d, the largest difference in total deaths between strategies occurs when there are 5000 vaccines available. While the optimal strategy is consistent, when there are more than 5000 doses available, we can vaccinate the entirety of Group 1 and begin to vaccinate Group 2. This is when we see the outcomes of poor and optimal strategies approach one another. As vaccine effectiveness increases, there is a large reduction in outcome for the optimal strategy, but a much smaller improvement for poor strategies. As vaccination only impacts infected people, vaccinating the less vulnerable, who are already unlikely to experience symptomatic or die due to infection, does little to reduce an



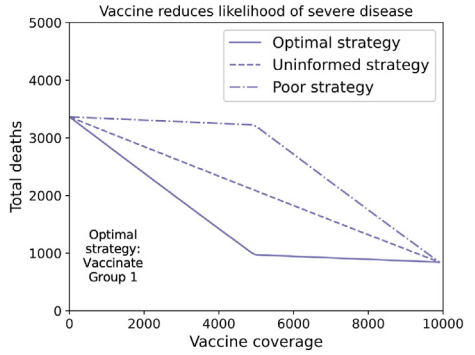
(a) Total **infections** for a vaccine that reduces susceptibility for three allocation strategies as we vary vaccine effectiveness.



(b) Total **infections** for a vaccine that reduces infectivity for three allocation strategies as we vary vaccine coverage.



(c) Total **symptomatic infections** for a vaccine that reduces the probability of developing symptomatic infection for three allocation strategies as we vary vaccine effectiveness.



(d) Total **deaths** for a vaccine that reduces the probability of dying due to infection for three allocation strategies as we vary vaccine coverage. Note the reduced scale for total deaths.

Fig. 3. Comparing the differences between strategies for varying vaccine mechanisms and allocation objectives as we vary vaccine effectiveness and coverage. Each figure gives an example of how the difference between the outcomes of optimal and suboptimal strategies change between vaccine mechanisms that impact transmission, and mechanisms that affect individual infection.

objective focused on these infection characteristics. That is, for a vaccine mechanism that *directly* impacts an objective, as we increase effectiveness of coverage (until one group is fully vaccinated) we see the best reduction in outcome for the optimal strategy, and little reduction for the poor strategy. In this scenario, allocating poorly with an effective vaccine or high coverage could result in a worse outcome than allocating well with an ineffective vaccine or lower vaccine coverage. This is also demonstrated in Figs. S19, S20, S23, S24 in the supplementary which show the difference between outcomes for vaccines that reduce probability of symptomatic infection or dying due to disease as we vary vaccine effectiveness and coverage.

4. Discussion

Our results demonstrate how the difference in outcomes of vaccination strategies depends on disease and vaccine characteristics as well as allocation objective considered. For disease characteristics that indirectly impact an objective, the difference in outcome between strategies depends on the individual parameter values for each population group. On the other hand, if a disease characteristic directly impacts the objective, the difference between outcomes of various strategies depends on the relative parameter values between each group. For a vaccine mechanism that indirectly impacts the objective, increasing vaccine efficacy or coverage results in better outcomes for all strategies. However, for a vaccine mechanism that directly impacts the objective, increasing vaccine efficacy or coverage does not guarantee a better outcome for all strategies. In this scenario, poor vaccine resources allocated well can result in a better outcome than good resources allocated poorly.

By investigating allocation strategies for individual vaccine mechanisms and objectives, we lay foundations for a model that considers multi-mechanism or multi-objective strategies. When designing vaccine strategies without knowing the specifics of the vaccine, modelling often assumes individual mechanisms, or simply that a vaccine provides reduced susceptibility (Matrajt et al., 2021a; Moore et al., 2021; Rao & Brandeau, 2021; Shim, 2021). When vaccines eventually become available and are observed to have multiple characteristics – against susceptibility, infectivity, and/or disease for example – appropriate mechanisms can be built into models and parameterised using effectiveness parameters derived from epidemiological/clinical data (Matrajt et al., 2021b; McVernon et al., 2021; Steyn et al., 2022). Our model incorporates multiple possible vaccine mechanisms, however we restrict our analysis to the impact of each separately.

Furthermore, we consider objectives that are not strictly independent of one another. Due to our model assumptions, reducing infections leads to a reduction in symptomatic infections which further leads to a reduction in deaths. However, by considering the direct and indirect impacts of vaccination, we can determine the effect of various disease and vaccine characteristics on the outcome of independent objectives. To consider allocation strategies for multiple objectives would require a single objective of weighted individual objectives. This weighted objective would allow us to consider the impact of vaccination on each individual part, as described in our results.

Our modelling is intentionally simple to understand infection dynamics when varying disease characteristics and vaccine mechanisms under various vaccination strategies. By choosing a well-studied and understood model (SEIR) and 2-group population structure, we can have confidence that our results are due to the scenarios we explored. This is opposed to using a more complex model, where it may be unclear if certain outcomes are due to the scenario or the complex model dynamics. However, our model is not intended to describe any one specific realistic scenario. When considering a more complex model structure or more population groups, we expect our results to hold under the same assumptions and when grouping population groups in the high risk vs low risk structure considered here.

While we have explored one aspect of vaccine strategy, i.e. disease and vaccine characteristics, there are many other aspects worth exploring. Our modelling describes pre-epidemic vaccination (i.e. before a disease is introduced, or at a point of low community prevalence), but timing of vaccine roll-out plays an important role in initial disease transmission (Albani et al., 2021a; Amaku, Covas, Coutinho, Azevedo, & Massad, 2021). Underreporting of infections at the beginning of an epidemic, as seen with COVID-19, also impacts the outcomes of vaccination strategies (Albani et al., 2021b; Lau et al., 2021). Furthermore, we assumed constant vaccine effectiveness across our population, but age dependent vaccine effectiveness has been observed, for example for influenza vaccines (Goodwin, Viboud, & Simonsen, 2006). When considered in the model, this may alter not only the optimal vaccination strategy, but also the difference between optimal and suboptimal strategies (Dushoff et al., 2007; Moore et al., 2021; Tuite, Fisman, Kwong, & Greer, 2010). More information and a model incorporating observed heterogeneities would be required to produce results for vaccination scenarios against a particular disease.

Our modelling provides a theoretical framework in which to ask questions about the outcomes of vaccination strategies as we vary disease and vaccine characteristics, and objective considered. Through considering individual vaccine mechanisms and objectives we can investigate their individual impact under various vaccination strategies. Given our model assumptions, this allows us to explore the idea of prioritising vaccine allocation over vaccine ascertainment: how will more effective vaccines or increased vaccine coverage improve our outcome for the current strategy? Would less effective vaccines or lower coverage perform better under a more optimal strategy? Our results highlight the importance of investigating how individual disease and vaccine characteristics impact the difference in outcomes between vaccination for the development of, or updating of, vaccine policies.

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Consent

All authors have given consent for publication of this article.

Code availability

The MATLAB code used to generate all results in this manuscript is available online https://github.com/iabell/vaccine_allocation.

Authors' contributions

All authors contributed to the planning of the work, interpretation of results and editing of the manuscript. IA implemented the methods, ran the simulations and wrote the first draft of the manuscript.

Declaration of competing interest

The authors have no competing interests to declare that are relevant to the content of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idm.2023.05.003.

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